

Biomedical Applications of Functionalized Carbon Nanotubes in Anticancer Drug Adsorption and Controlled Release

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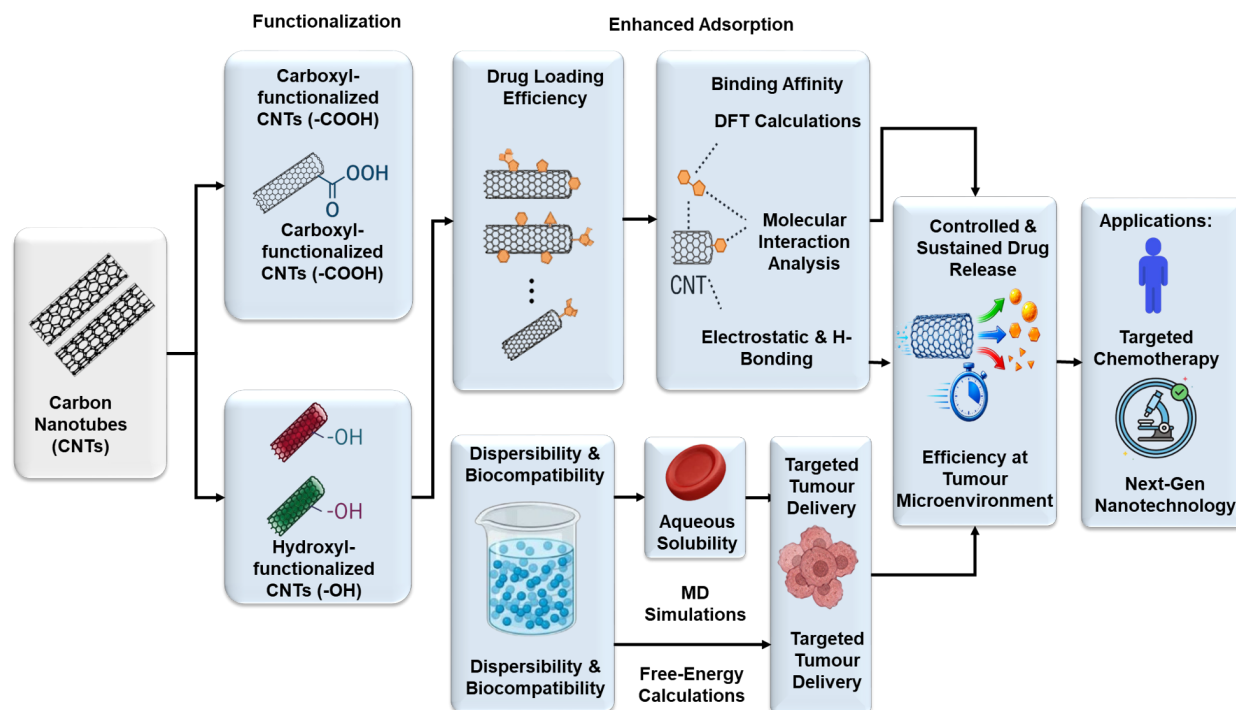
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Abstract

Carbon nanotubes (CNTs) have appeared as promising nanocarriers for advanced anticancer drug delivery due to their high surface area, unique structural properties, and excellent adsorption capability. Inadequate adsorption and uncontrollable release behavior limit traditional anticancer medication delivery methods. Research investigates the biomedical applications of functionalized CNTs for anticancer medication adsorption and controlled release in physiological environments. Carboxyl- and hydroxyl-functionalized CNTs were evaluated as potential nanocarriers to enhance the loading efficiency, aqueous solubility, and targeted delivery of anticancer drugs. Density Functional Theory (DFT) calculations and molecular interaction analyses were employed to examine the adsorption behavior and binding affinity between anticancer drug molecules and functionalized CNT surfaces. Furthermore, Molecular Dynamics (MD) Models and free-energy calculations were utilized to investigate the stability, intermolecular interactions, and release characteristics of drug-loaded CNT systems in aqueous media. Functionalized CNTs exhibited the largest charge transfer (0.196 e) and enhanced adsorption (-67.25 kcal/mol for (Carboxyl-Functionalized Multi-Walled Carbon Nanotubes (MWCNT-COOH)). Superior stability was demonstrated by MD analysis, with a (Root Mean Square Deviation (RMSD) 0.26 nm, a Solvent Accessible Surface Area (SASA) 19.6 nm². At pH 5.5, pH-responsive release reached 91.2%, demonstrating effective tumor-targeted controlled drug delivery efficacy. The findings suggest that functionalized carbon nanotubes possess substantial potential as efficient nanocarriers for targeted chemotherapy, controlled drug release, and next-generation biomedical nanotechnology applications in cancer treatment.

Keywords: *Controlled Drug Release, Nanomedicine, Molecular Dynamics Simulation, Binding Affinity, targeted drug delivery, Physiological Environment.*

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1. Introduction

The growth of nanotechnology is revolutionizing the field of biomedicine. The pharmacokinetics and pharmacodynamics of

medicinal drugs are made more efficient through the use of nanotechnology. Moreover, the nano systems deliver advanced distribution, biological stability, reduced side properties, and extended medication

distribution [1]. In the field of biomedicine, Carbon Nanotubes (CNTs) are gaining much popularity because of their ability to serve as an excellent drug delivery, diagnostics, and imaging agent. Their versatile structures like Single-Walled Carbon Nanotubes (SWCNTs) and Multi-Walled Carbon Nanotubes (MWCNTs) can be modified with dissimilar functional polymers, which help them in their drug-loading capacity and distribution [2]. The SWCNTs contain of a solitary coating of hexagonal rings that range in length from 5 to 10 μm and have a 1-2 nm diameter. The MWCNTs consist of numerous cylindrical graphene areas having different diameters ranging from 2 to 25 nm and an inter-layer distance of about 0.35 nm. The different types of CNTs include chiral (n,m), arm-chair (n,n), and zigzag (n,0). As a result of their high loading capacity, pH-sensitive discharge, and prolonged circulation, the SWCNTs are considered to be potential tools for cancer diagnostics and treatment [3, 4]. Because of their many functionalization sites, superior stability, increased rigidity for a large drug loading capability, and decreased danger of drug leakage, MWCNTs are chosen over SWCNTs [5]. In terms of structure, CNTs are cylindrical nanostructures made of revolved graphene masses that provide a sizable and adjustable external part that promotes effective medication transport. Cellular absorption and transport of several therapeutic compounds, including Small Interfering Ribonucleic Acid (siRNA), proteins, and chemotherapeutic drugs, are made possible by their needle-like form [6]. Functional groups like hydroxyl ($-\text{OH}$) and carboxyl ($-\text{COOH}$) were used extensively to optimize drug adsorption and release behavior, and improve CNT dispersion in aqueous conditions [7]. Nevertheless, their hydrophobicity and toxicity pose difficulties, including self-aggregation problems that impede the encapsulation of biomolecules. To successfully increase intracellular concentrations, functionalizing CNTs is essential for enhancing effectiveness, biocompatibility, and cellular uptake of pharmaceuticals [8, 9]. Figure 1 illustrates enhanced delivery efficiency, biocompatibility, and targeted delivery to cancer cells through ligand-modified nanotubes. In addition, it demonstrates the distribution of anti-cancer painkillers over CNTs, which includes loading of drugs, targeting tumor cells, and issue of the drug.

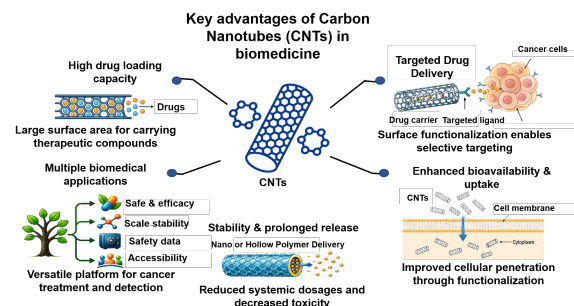


Figure 1: Functionalized CNTs-Based Targeted Medication Distribution and Cellular Acceptance Mechanism

In several biological domains, such as medication distribution, hereditary manufacturing, imaging, and biosensing to pleasure and detect a range of malignancies, CNTs are emerging stars. Therefore, functionalizing CNTs with various chemical groups or biomolecules to increase hydrophilicity and decrease cytotoxicity is crucial to improving safety and effectiveness for widespread use in cancer therapy [10]. Graphene sheets composed of sp^2 crossed carbon particles with heavy tubes are architecturally present in CNTs, which are artificial carbon nanomaterials. The electron microscopic construction demonstrates that modified water-soluble CNTs can readily overcome biological barriers without producing adverse effects and do not hinder any active drug groups when used in gene and drug delivery [11]. CNTs have a variety of applications due to

- (i) Its tubular structure having a big superficial zone makes it perfect for drug delivery.
- (ii) Its hydrophobic nature making it more feasible for the delivery of biomolecules, and
- (iii) Its excellent optical properties enable the utilization of a contrast agent, photodynamic therapy, and photoacoustic imaging [12].

By increasing cell penetration and facilitating selective targeting in anticancer treatments through surface functionalization, CNTs enhance drug delivery. They improve scaffolds' mechanoelectrical qualities in tissue engineering, promoting chemical processes inside cells [13, 14]. Covalent and non-covalent functionalization are the two primary methods for functionalizing carbon nanotubes. Covalent functionalization, such as adding carboxylic acid or hydroxyl groups, is a promising method for increasing the usage of CNTs as a medication distribution scheme due to their advantages and ease of control [15]. Factors such as toxicity, aggregation, synthesis, and low biocompatibility hinder the application of CNTs in medicine due to their great medicine packing, large external zone, and possible as a carrier of drugs for targeted cancer treatment. Functionalization helps deliver drugs in a more efficient way, reduces toxicity, improves dispersion,

and also increases the selectivity towards cancer cells [16]. Table 1 shows dissimilar kinds of functionalization used to improve the efficacy of CNTs in anticancer medicine distribution schemes. Dispersion, biocompatibility, attachment, and drug loading are achieved through surface modifications, such as $-\text{COOH}$, $-\text{OH}$, $-\text{NH}_2$, polymers, and targeting ligands.

Table 1: Functionalization Strategies and Their Effects on CNTs-Based Drug Delivery Systems

Functionalization Type	Functional Group	Primary Purpose	Impact on Drug Delivery
Oxidative Functionalization	$-\text{COOH}$	Increase hydrophilicity and active binding sites	Improves drug adsorption and aqueous dispersion
Hydroxyl Functionalization	$-\text{OH}$	Enhances surface polarity	Facilitates hydrogen-bond interactions with drugs
Amination	$-\text{NH}_2$	Introduce positive surface charge	Promotes electrostatic interactions and cellular uptake
Polymer Functionalization	PEG, Chitosan	Improve biocompatibility and circulation time	Reduces aggregation and prolongs drug retention
Ligand Functionalization	Folic acid, Biotin	Target cancer-specific receptors	Enhances selective tumor accumulation

Dual Functionalization	Combination of multiple groups	Achieve multifunctionality	Improves loading efficiency, stability, and controlled release
Sulfonation Functionalization	$-\text{SO}_3\text{H}$	Increases water solubility and surface reactivity	Enhances dispersion and facilitates drug conjugation
Surfactant-Assisted Functionalization	SDS, Tween-80, Triton X-100	Prevent nanotube aggregation	Improves colloidal stability and increases drug-loading efficiency

Research aim and contributions

Using Density Functional Theory (DFT), Molecular Dynamics (MD) recreations and Molecular Mechanics/Poisson-Boltzmann Surface Area (MM/PBSA) techniques, this study tries to evaluate the performance of functionalized Multi-Walled Carbon Nanotubes (MWCNTs) in terms of carrying anticancer drugs with better stability and pH-sensitive drug delivery.

- ❖ Functionalization of MWCNTs (functionalization of MWCNTs with $-\text{OH}$ and $-\text{COOH}$ groups) are carried out for making the solubility of the anticancer drugs better.
- ❖ Electronic structure, binding energy and reactivity were determined by DFT techniques.
- ❖ The stability, binding energy and thermodynamic studies were performed using MD simulation and MM/PBSA technique.
- ❖ Controlled and targeted drug delivery can be done through a pH sensitive drug release mechanism.

Research organization: Introduction and objectives of CNTs medication transfer systems are deliberated in Section 1. Nanocarrier-related work and related works are discussed in Section 2. Methodology, which involves MM-PBSA calculation and DFT molecular dynamics simulation, is discussed in Section 3. Structural, electronic adsorption, and desorption results are discussed in Section 4. Literature gaps were discussed in Section 5 and Section 6 accomplishes the research.

2. Related works

Previous research has shown that nanocarriers are effective, but greater examination is needed into molecular interactions, adsorption stability, and release processes.

For targeted cancer treatment delivery, carbon nanospheres were created by Chemical Vapor Deposition (CVD) and functionalized with Polyethylene Glycol (PEG), and curcumin [17]. The system demonstrated 63.63% loading efficiency and sustained pH-responsive release, although its release efficiency and pH sensitivity deteriorated over time. To administer neratinib in breast cancer treatment, biotinylated chitosan-coated carboxylate multiwalled CNTs were created as dual-targeted carriers [18]. The formulation demonstrated improved cytotoxicity against breast cancer cells and 95.6% drug loading.

To administer quercetin in anticancer therapy, a hydrogel nanocomposite of chitosan, carboxymethyl cellulose, and CNTs was created [19]. Sustained release and increased cytotoxicity against MCF-7 cells were made possible by the system's improved drug loading (48%) and encapsulation (86.5%). 1, 2-Distearoyl-sn-Glycero-3-Phosphoethanolamine-Poly (Ethylene Glycol)-Carboxylic Acid (DSPE-PEG-COOH), and ethylenediamine were developed to create double-functionalized SWCNTs for the transfer of EGFP plasmid and amphotericin B [20]. X-ray Photoelectron Spectroscopy (XPS) revealed a rise in oxygen (2.3–22.5%) and a decrease in carbon (97.2–69.9%).

Curcumin (CUR) and Methotrexate-Bovine Serum Albumin (MTX-BSA) can be co-delivered in a stimuli-responsive manner using functionalized MWCNTs (β -MWCNTs) [21]. Successful formulation was validated by characterization using Dynamic Light Scattering (DLS), and Differential Scanning Calorimetry (DSC). For the purpose of delivering anticancer drugs, β -MWCNTs (CNT-COOH and CNT-NH₂) were coated with chitosan-stearic acid and dual-loaded with Ferulic Acid (FUA) and Diosgenin (DGN) [22]. Through the modification of lncRNAs, microRNAs, and proteins, the formulation demonstrated glutathione-responsive sustained release and increased apoptosis in HepG2 cells.

MD simulations were used to assess Carboxyl-Functionalized Carbon Nanotubes (CNT-COOH) as Doxorubicin (DOX) transporters. Drug stability and loading were enhanced by increasing COOH functionalization from 2.5% to 10% [23], which also decreased Mean Squared Displacement (3.42–3.24 Å²), Root Mean Square Deviation (1.85–1.80 Å), and structural density (0.0035–0.0042 atm/Å³). Atomistic Molecular Dynamics calculations were used to study Tryptophan-coated CNTs (TRP@CNTs) as pH-sensitive nanocarriers for Topotecan delivery [24]. Tryptophan improved the biocompatibility and solubility of CNTs, and acidic tumor-like environments encouraged regulated drug release via electrostatic repulsion.

A CNTs/Ordered Mesoporous Carbon/Chitosan (CNTs/OMC/CS) nanocomposite was prepared for battered transfer of Everolimus (EVE) to lung tumor cells. The carrier exhibited pH-responsive drug release with a level of 88.0% at pH 4.5 within 25 hours and achieved 89.4% of drug loading [25]. Since it had an inferior IC₅₀ value (~9 µg/mL) compared to free EVE (~13 µg/mL), it showed more efficient anticancer activity against A549 cells. The adsorption of daunorubicin on carboxylated SWCNTs was found to be quite effective, exhibiting maximum adsorption energy of -68.553 kcal/mol according to Density Functional Theory (DFT) controls [26]. The potential use of COOH-functionalized and N-doped SWCNTs for targeted delivery of anticancer drugs was highlighted by increased hydrogen bonding, exothermic adsorption, and release of drugs at low pH.

For regulated heparin release from metallic implants, a polymer-free MWCNT-based covering containing iron nanoparticles was created [27]. The coating demonstrated magnetically initiated and sustained drug delivery by lowering burst release from >95% to 77.26% in under one hour and allowing an extra 7.16% drug release under a 30 mT, 95 kHz magnetic field. A Box-Behnken design was adopted to optimize the decorated Multi-Walled Carbon Nanotubes-carboxylation of citric acid (MWCNT-COOH-CA) in the delivery of curcumin as an anti-breast cancer drug [28]. A formulation that achieved a 371 nm size of nanoparticles, 77.86% entrapment efficiency, and pH-sensitive release (93.48% at pH 5.5) was obtained. The Targeting ability of the formulation towards cancer cells was validated through increased cellular uptake and significant cytotoxicity on MCF-7 cells (IC₂₀ = 30.8).

Aluminum-doped boron nitride nanosheets (Al₃B₂₁N₂₄ and Al₄B₂₂N₂₄) showed high gemcitabine adsorption with energies of -86.74 and -92.50 kcal/mol in air, according to DFT experiments [29]. It was established based on the enhanced stability of such materials in water, favorable solvation, and

pronounced UV-visible spectroscopic changes. Increasing the density (from 0.0033 to 0.0036 atm/Å³) and reducing shear stress (from 3.25 to 3.11 Pa) and temperature (from 391.91 to 368.77 K) at higher pH levels (3 to 11) enhanced structural stability [30]. The findings revealed better drug stability and controlled pH-responsive release, which indicated the possibility of the use of such materials as drug nanocarriers.

The adsorption of drugs (doxorubicin and camptothecin) onto SWCNTs was investigated via density functional-based tight-binding calculation [31]. It was shown that size, chirality, and length of nanotubes significantly affected the efficiency of loading, structural stability, and interaction. The effectiveness of functionalized CNTs as a potential carrier of the anticancer drug imatinib was analyzed [32]. Reversible physical adsorption π - π -stacking was detected with a more stable complex with Azacitidine.

The use of CNTs for encapsulation of methylene blue, and doxorubicin for targeting of drugs to treat cancer cells was explored by using mathematical derivation and the Unified Non-dominated Sorting Genetic Algorithm III (U-NSGA-III) optimization method [33]. Not only was the cost of computation significantly reduced, but the optimal values for tube radii and equilibria were found, which helped understand the controlled release mechanism. The possibility of using BC3 nanotubes for melphalan delivery, which is a cancer drug, was studied by conducting periodic density functional theory computations using the Becke, three-parameter, Lee–Yang–Parr (B3LYP) and Minnesota 2006 with double exchange (M06-2X) functionals [34].

3. Methodology

The carboxyl (-COOH) and hydroxyl (-OH) groups were incorporated into the surface external of MWCNTs to improve their physical and chemical properties for carrying anticancer drugs. The interactions among molecules, evaluation of electronic structures, modeling of adsorption processes, and geometrical optimizations have been analyzed. Besides, the adsorption properties and controlled drug release capability have been studied under physiological conditions via MD models and free energy design. The sequential process from CNT synthesis to DFT modeling and subsequent MD simulation, is showed in Figure 2.

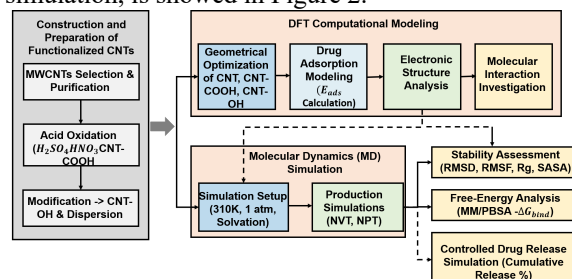


Figure 2: Workflow of the functionalized CNTs-based drug delivery

3.1 Construction of CNTs Models

Initially, the base nanocarrier model for anticancer drug delivery applications was a pristine CNT nanostructure. The CNTs' sidewalls were then surface functionalized by adding -OH and -COOH groups to enhance hydrophilicity, dispersibility, and active adsorption sites for drug binding. DFT imitations were used to fully enhance the geometry of the resulting functionalized nanocarriers, known as CNT-COOH and CNT-OH, to produce energetically stable topologies with reduced atomic forces and total energy. Under physiological settings, the optimized structures were also used for studies on adsorption, contact, and controlled drug release. The impact of functionalization-induced modifications in bond lengths, charge distribution, and active adsorption sites on anticancer drug loading capacity, intermolecular interactions, and nanocarrier performance in biomedical drug delivery applications was also investigated in this research.

3.2 Construction and Preparation of Functionalized CNTs

The selection of MWCNTs [35] was based on their larger surface area, several concentric graphene sheets, higher mechanical strength, and higher drug loading capacity than SWCNTs. The nanocarrier material was selected to be MWCNTs having diameters of 10–20 nm, a length of 5–15 μm, and clarity above 95%. At first, a 3:1 (v/v) solution of concentrated H₂SO₄ (98%) and HNO₃ (70%) was used to purify and oxidize the pristine MWCNTs at a temperature of 70–80 °C for 4–6 hours under continuous stirring using a magnetic stirrer. By this process, oxygen-containing functional collections were introduced to the nanotube external, and all the catalyst materials were removed from the nanotubes.

The oxidized nanotubes were dehydrated in a hot-air oven at 60 °C for 12 h later washing the samples with deionized water periodically to reach a neutral pH, which is 7.0. The prepared carboxyl-functionalized CNT (CNT-COOH) was then modified by controlling surface hydroxylation to synthesize hydroxyl-functionalized CNT (CNT-OH). For preparing a homogeneous solution, these functionalized CNTs were ultrasonically dispersed in distilled water for 30 min at 40 kHz. The CNT-COOH and CNT-OH samples were obtained via centrifugation at 10,000 rpm for 15 minutes following functionalization, while the samples were repeatedly rinsed using deionized water to remove any acids and contaminants. To obtain the stable powder, the functionalized CNT samples were dried using a vacuum technique for 24 hours at 70 °C. Prior to drug-

loading experiments, the dried CNT samples were stored under ambient conditions in sealed vials.

3.3 Modeling of Drug Absorption

Nanocomplexes of drug-MWCNT, drug-MWCNT-COOH, and drug-MWCNT-OH [36] were prepared for the investigation of drug adsorption conduct of selected anticancer treatment molecules on virgin and functionalized CNTs. To determine the optimal adsorption site, first the optimized drug molecules were placed above the nanotube surface at various orientations with an initial distance between 2.0 and 4.0 Å. Next, geometry optimization of each complex was done through DFT calculations at 298 K and 1 atm. To measure the degree of contact among the medication particle and the nanotube external, the adsorption energy (E_{ads}) were calculated in Equation (1).

$$E_{ads} = E_{complex} - (E_{CNT} + E_{drug})$$

(1)

Where E_{drug} is the energy of the secluded medicine therapy, E_{CNT} denotes the energy of the secluded nanotube, and $E_{complex}$ is the overall vigor of the drug-CNT combination. Stronger and more stable adsorption was indicated by larger negative adsorption energy values. To identify the predominant adsorption process, contact distances, hydrogen-bond lengths, charge transfer, and binding orientations were also assessed.

3.4 Electronic Structure Analysis

DFT computations were achieved to investigate the automated possessions of the optimized nanocomplexes of the drug with MWCNT, drug with MWCNT-COOH, and drug with MWCNT-OH to understand the result of the surface functionalization on the adsorption and binding assets of the drug [37]. The stability and chemical reactivity of the nanocomplexes were analyzed through the calculation of the energy values of the Highest Occupied Molecular Orbital (HOMO) and Lowest Unoccupied Molecular Orbital (LUMO), respectively, and the energy gap ($\Delta E = E_{LUMO} - E_{HOMO}$). Stronger interaction between the anti-cancer drug and the functionalized CNT surface was indicated by a lower value of the HOMO-LUMO energy gap.

Additionally, the delivery of automated conditions near to the Fermi equal and the alterations in the electronic structure brought about by drug adsorption were investigated using the Density of States (DOS) [38] examination. To identify possible adsorption sites and intermolecular interaction zones, electron-rich and electron-deficient regions were shown using Molecular Electrostatic Potential (MEP) charts. To determine the influence of carboxyl and hydroxyl functionalization on adsorption strength,

obligatory affinity, and nanocarrier stability, the electronic parameters derived from MWCNT, MWCNT-COOH, and MWCNT-OH systems were compared.

3.5 Molecular Interaction Investigation

To understand the process of adsorption and stability, the nature of interactions between the molecules of the anticancer drugs and the carriers (CNT, CNT-COOH, and CNT-OH) was investigated. Molecular Electrostatic Potential (MEP), Mulliken charge analysis, electron density distribution, and NCI calculations were performed to study the optimized nanostructures. Hydrogen bonds were established between the polar regions of pharmaceuticals and oxygenated functional groups, wherein the bond length was always in the range of 1.5 to 3.5 Å. Charge transfer across the interface was calculated to measure electrostatic connections; however, van der Waals and π - π stacking governed the connections of aromatic rings of pharmaceuticals with the CNTs' surface. The stability of the system was evaluated using a correlation between adsorption energies and charge transfer and intermolecular distances.

3.6 Free-Energy Analysis

Under physiological settings (310 K, 37 °C, 1 atm), the MM/PBSA modal [39] was used to assess the binding affinity and thermodynamic equilibrium of drug-loaded CNT, CNT-COOH, and CNT-OH systems. Van der Waals, electrostatic, and solvation energy effects were examined. Stronger drug adsorption was indicated by more negative binding free energies, and functionalized CNTs showed improved stability as a result of advantageous hydrogen-bonding and electrostatic interactions. The binding free energy was computed in Equation (2).

$$\Delta G_{bind} = \Delta E_{vdW} + \Delta E_{ele} + \Delta G_{polar} + \Delta G_{nonpolar}$$

(2)

Where ΔE_{vdW} and ΔE_{ele} denote the electrostatic and van der Waals energies, respectively, whereas ΔG_{polar} and $\Delta G_{nonpolar}$ relate to the energies of solvation. More negative ΔG_{bind} is the data showed that the functionalized CNT nanocarriers have improved thermodynamic stability and stronger drug adsorption.

3.7 Molecular Dynamics (MD) Simulation Setup

The optimized drug-loaded CNT, CNT-COOH, and CNT-OH nanocomplexes were submerged in a particular aqueous solvation system using water molecules to replicate physiological biological circumstances. To recreate the behavior of the bulk solvent, the systems were put inside a periodic boundary condition box and charged by appropriate counter ions. Conditions such as temperature at 310 K, or about 37°C and pressure at 1 atm were kept under physiological conditions corresponding to human

body conditions. Temperature was controlled by a thermostat to ensure thermal stability, and pressure was controlled by a barostat

Initially, energy minimization was carried out on all systems to reduce undesired interactions and steric hindrance between atoms. After that, the temperature was set to 37 °C, pressure was set to 1 atm, and the system density was stabilized by using NVT (constant volume-temperature) and NPT (constant pressure-temperature) ensembles. Equilibrated structures were necessary for evaluating the structural stability, intermolecular interactions, and the efficiency of controlled drug delivery in production simulations.

3.8 Stability Assessment

The trajectory-based approach was applied to investigate the stability of drug-loaded CNT [40], CNT-COOH, and CNT-OH nanocarriers under physiological conditions (310 K and ~37°C and 1 atm). For monitoring the conformational stability and structural changes over time of the nanocomposites in the course of simulation, the Root Mean Square Deviation (RMSD) was estimated. Root Mean Square Fluctuation (RMSF) was determined to analyze the flexibility of each residue in the CNTs' backbone following the drug binding. To check the stability and compactness of the nano-carrier structures during the course of the simulation, the Radius of Gyration (Rg) was calculated. The low value of Rg indicated more stability and compactness of the nano-carriers. Solvent Accessible Surface Area (SASA) was measured to quantify the extent of drug-solvent and nano-carrier-solvent exposure, as it indicated the variation in surface hydrophilicity and exposure.

3.9 Controlled Drug Release Simulation

The release profile of anticancer drugs from the CNT, CNT-COOH, and CNT-OH carriers in physiological (pH 7.4, 310 K, 37 °C) and acidic (pH 5.5–6.5, tumor mimicry) conditions was analyzed. The effects of the COOH and OH groups on the dissociation and release kinetics were studied by observing the reaction and diffusion process throughout the simulation period. The fraction of cumulative drug release was determined in Equation (3).

$$\text{DrugRelease}(\%) = \frac{N_u}{N_\infty} \times 100$$

(3)

Where N_u symbolizes the quantity of medication released at time u , and N_∞ indicates the how much medication is loaded overall. Because of hydrogen bonding and electrostatic interactions, functionalized CNTs demonstrated improved pH-responsive and prolonged release behavior, allowing for effective drug release in acidic tumor surroundings, while

maintaining higher drug retention under normal physiological circumstances, according to a comparison.

4. Result

Geometrical, electrical, adsorption, and thermodynamic properties of both pristine and functionalized MWCNTs are analysed in this section. The Mechanisms of drug interactions, structural stability, and pH-controlled release processes for effective anticancer drug delivery systems are also studied employing DFT, MD, and MM/PBSA approaches.

4.1 Geometrical Characteristics and Surface Properties of Functionalized MWCNTs

The adsorption capability and efficiency of CNTs in medication transfer are highly dependent on the organic and bodily assets of the surface and structure of these nanotubes. Presenting oxygen-covering collections to the surface leads to the modification of the bodily and biochemical assets of MWCNTs, such as making them more hydrophilic and increasing their surface polarity.

The structural characteristics of both pristine and functionalized MWCNTs are compiled in Table 2 and Figure 3. Surface treatment raised the C–C bond distance from 1.42 Å to 1.44 Å and the nanotube diameter from 12.6 nm to 13.1 nm. For MWCNT–COOH, the functional group density reached 6.5%, producing a negatively charged surface. These modifications increased surface polarity and produced more active sites that are advantageous for effective drug adsorption and dispersion.

Table 2: Geometrical Parameters of Functionalized MWCNT Models

Syste m	Diam eter (nm)	Len gth (nm)	C–C Bon d Len gth (Å)	Functi onal Group Densit y (%)	Surfa ce Char ge
MWC NT	12.6	10.2	1.42	0	Neutr al
MWC NT– OH	12.8	10.2	1.43	4.8	Slight ly Negat ive
MWC NT– COOH	13.1	10.2	1.44	6.5	Negat ive

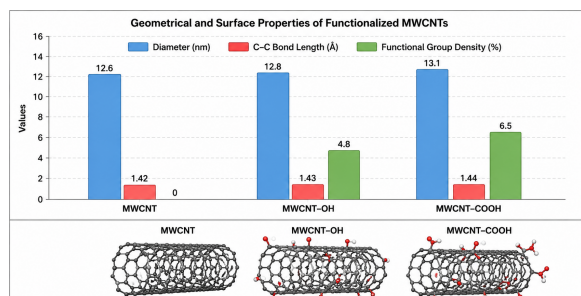


Figure 3: Geometrical and surface property evolution of functionalized MWCNT structures comparison

4.2 Frontier Molecular Orbital and Global Reactivity Analysis

Surface functionalization dramatically changed the electronic characteristics of MWCNTs, as shown by the frontier molecular orbital analysis in Table 3. The HOMO–LUMO vigor gap of pristine MWCNT was 2.67 eV, but it was lowered to 2.32 and 1.93 eV, respectively, by hydroxyl and carboxyl functionalization. Increased chemical reactivity was demonstrated by the drop in chemical hardness from 1.34 to 0.97 eV. Additionally, MWCNT–COOH's higher electronegativity (4.65 eV) indicated better electron-accepting capacity, encouraging stronger interactions with anticancer drug molecules and improving adsorption performance.

Table 3: Automated descriptors gained from DFT controls

Syste m	EHO MO (eV)	ELU MO (eV)	ΔE gap (eV)	Che mica l Hard ness η (eV)	Electrone gativity χ (eV)
MW CNT	−5.92	− 3.25	2.6 7	1.34	4.58
MW CNT −OH	−5.73	− 3.41	2.3 2	1.16	4.57
MW CNT − COO H	−5.61	− 3.68	1.9 3	0.97	4.65

4.3 Adsorption Configuration and Interfacial Binding Characteristics of Drug–MWCNT Nanocomplexes

Table 4 shows the relative contributions of intermolecular interactions to drug-loaded MWCNT systems' stability. With total stabilization energy of −38.72 kcal/mol, pristine MWCNT showed

stabilization mainly due to π – π connections (48.6%) and van der Waals forces (38.6%). With MWCNT–COOH exhibiting the largest hydrogen-bond contribution (41.3%) and strongest stabilization energy (−67.25 kcal/mol), indicating improved adsorption performance and binding equilibrium, surface functionalization greatly increased hydrogen-bonding and electrostatic contributions.

Table 4: Contributions of Intermolecular Interactions to Drug Adsorption Stability

Surf ace Syst em	π – π Inter action Contr ibutio n (%)	Hydr ogen Bond Contr ibutio n (%)	Electr ostati c Contr ibutio n (%)	van der Waal s Contr ibutio n (%)	Total Stabil izatio n Ener gy (kcal/ mol)
MW CNT	48.6	0.0	12.8	38.6	– 38.72
MW CNT −OH	31.4	35.7	18.6	14.3	– 55.84
MW CNT − CO OH	22.5	41.3	25.8	10.4	– 67.25

4.4 Active Binding Site Identification and Interaction Mechanism Mapping

Adsorption properties of pharmacological compounds on pristine and modified MWCNTs are summarized in Table 5. The π – π stacking of pharmacological compounds is observed between the pristine MWCNT and its graphitic carbon surface, where the average distance is 3.18 Å, indicating moderate binding affinity. Drug attachment is enhanced after the surface functionalization due to increased number of intermolecular interactions. The distance for the MWCNT-OH hydrogen bond is 2.61 Å, whereas the distance for MWCNT-COOH is the lowest, with a value of 2.34 Å due to hydrogen and electrostatic interactions. Because of the smallest interaction distance and simultaneous electrostatic-hydrogen bonding, MWCNT–COOH showed improved binding.

Table 5. Active Adsorption Sites and Dominant Stabilization Mechanisms

Funcio nalized Surface	Maj or Acti	Drug Func tiona l	Aver age Inter actio	Domi nant Stabili zation	Rela tive Bin ding
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	ve Site	Group Involved	n Distance (Å)	Mechanism	Strength
MWCNT	Graphitic carbon surface	Aromatic ring	3.18	π - π stacking	Moderate
MWCNT-OH	Hydroxyl oxygen	Carbonyl group	2.61	Hydrogen bonding	Strong
MWCNT-COOH	Carboxyl oxygen	Amine and carbonyl groups	2.34	Electrostatic + H-bonding	Very Strong

4.5 Interaction Energy Decomposition and Thermodynamic Stabilization Profile

Dispersion interactions play a predominant role in the Drug/MWCNT system, whereas functionalization significantly enhances the Coulombic and polar interactions, based on the findings of the interaction energy decomposition analysis, shown in Table 6 and Figure 4. The thermodynamically more stable nature is evident from the highly negative net interaction energy values (-55.87 to -67.48 kcal/mol) for MWCNT-OH and MWCNT-COOH systems. Increased polar interaction energy values show better hydrogen bonding and electrostatic interactions, whereas reduced nonpolar interaction energy values indicate good surface polarity for drug binding. With the highest negative interaction energy (-67.48 kcal/mol), drug/MWCNT-COOH demonstrated the highest thermodynamic stability.

Table 6. Interaction Energy Decomposition of Drug-Loaded MWCNT Systems

System	Dispersion Energy (kcal/mol)	Coulombic Energy (kcal/mol)	Polar Interaction Energy (kcal/mol)	Nonpolar Interaction Energy (kcal/mol)	Net Interaction Energy (kcal/mol)
MWCNT	25.36	-8.72	6.15	-	-
MWCNT-OH	31.44	-15.28	9.37	-	-
MWCNT-COOH	36.82	-22.41	11.64	-	-

Drug/MWCNT	25.36	-8.72	6.15	-	-
Drug/MWCNT-OH	31.44	-15.28	9.37	-	-
Drug/MWCNT-COOH	36.82	-22.41	11.64	-	-

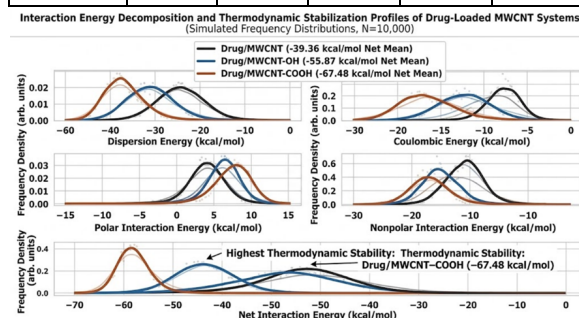


Figure 4: Interaction Energy Decomposition and Thermodynamic Stabilization Profiles of MWCNT Systems

4.6 Interfacial Interaction and Binding Enhancement via Surface Functionalization

As demonstrated by the comparative analysis in Table 7, surface modification enhances the interaction between the drug and nanocarrier considerably. Since pristine MWCNT has an enhanced contact distance of 3.18 Å and no hydrogen bond interaction, its binding ability and adsorption energy are less efficient (-38.72 kcal/mol). The functionalization process involving carboxyl and hydroxyl groups enhances hydrogen bonding and charge transfer interaction while minimizing the contact distance to 2.34 Å and 2.61 Å, respectively. This results in enhanced adsorption ability (154%) for MWCNT-COOH.

Table 7: Surface Functionalization Effect on Drug Binding Performance

Parameter	MWCNT	MWCNT-OH	MWCNT-COOH
Contact Distance (Å)	3.18	2.61	2.34
Number of Hydrogen Bonds	0	2	3
Charge Transfer (e)	0.081	0.143	0.196
Adsorption Energy (kcal/mol)	-38.72	-55.84	-67.25

Relative Drug Loading Efficiency (%)	100	129	154
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4.7 Molecular Dynamics-Based Structural Stability Assessment

Based on the results in Table 8 obtained from the MD simulation, functionalization is an vital character in stabilizing the nanocarrier. Having the lowest RMSD value (0.26 nm), RMSF value (0.14 nm), radius of gyration (1.54 nm), and SASA (19.6 nm²) indicates the highest level of stability and compactness for the Drug/MWCNT-COOH system. In comparison with virgin and hydroxylated CNT systems, lower fluctuation and reduced solvent exposure indicate improved drug retention and stability.

Table 8: Structural Stability Parameters from MD Simulation

Parameter	Drug/MW CNT	Drug/MW CNT-OH	Drug/MW CNT-COOH
Average RMSD (nm)	0.41	0.32	0.26
Average RMSF (nm)	0.22	0.18	0.14
Radius of Gyration (nm)	1.82	1.69	1.54
SASA (nm ²)	26.7	22.8	19.6

Surface functionalization significantly enhances the stability of MWCNT structures based on the findings of MD simulations. Compared to functionalized MWCNTs, functionalized MWCNTs display lower variations in the structure, meaning enhanced stiffness (Figure 5(a)). The lower residues' fluctuation, particularly for the Drug/MWCNT-COOH, can be seen in Figure 5(b); thus, the interactions are stronger and stable. Higher density, which implies denser packed structure due to modification, is shown in Figure 5(c). Lower solvent exposure in Figure 5(d) means better shielding against the environment. In summary, surface functionalization results in the enhancement of stability, flexibility, and drug-nanocarrier interaction.

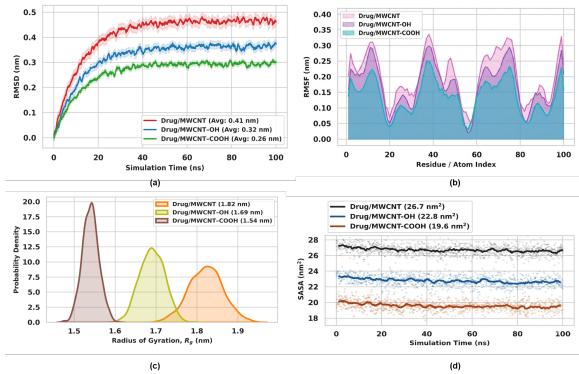


Figure 5: Functionalized Nanocarrier Dynamics of (a) System Stability, (b) Atomic Flexibility, (c) Molecular Compactness, and (d) Solvent Exposure

4.8 Binding Free Energy and Thermodynamic Stability Evaluation

The Molecular Mechanics/Poisson-Boltzmann Surface Area (MM/PBSA) data in Table 9 show that functionalization improves the thermodynamic stability of drug-CNT complexes. Enhanced interaction between the molecules is reflected in the enhanced value of electrostatic (ΔE_{ele}) and van der Waals (ΔE_{vdW}) energies in COOH-functionalized CNTs' than in the pure CNT. In the case of functionalized nanosystems, non-polar and electrostatic interactions dominate, and therefore the stability of the drug is enhanced.

Table 9: MM/PBSA Energy Components

Energy Component	Drug/MWCNT	Drug/MW CNT-OH	Drug/MW CNT-COOH
ΔE_{vdW} (kJ/mol)	-134.5	-168.3	-201.4
ΔE_{ele} (kJ/mol)	-41.6	-69.2	-88.5
ΔG_{polar} (kJ/mol)	63.1	72.4	81.6
$\Delta G_{non polar}$ (kJ/mol)	-15.4	-19.1	-22.7

4.9 pH-Responsive Controlled Drug Release Behavior of Functionalized MWCNT Systems

All nanocarrier technologies exhibit considerable pH-dependent behavior in their cumulative drug release patterns, shown in Table 10 and Figure 6. Drug release is nonetheless reduced at physiological pH 7.4 because of weak desorption

kinetics and persistent π - π stacking interactions, especially in MWCNT-COOH systems. Protonation increases hydrogen bond breakdown and electrostatic repulsion under acidic tumor-like circumstances (pH 5.5), greatly boosting release rates. Tumor-specific release efficiency is enhanced in functionalized systems.

Table 10: Cumulative drug release under physiological and tumor conditions

pH	Complex	Release after 24 h (%)	Release after 48 h (%)
7.4	Drug/MWCNT	32.4	47.2
	Drug/MWCNT-OH	25.6	39.8
	Drug/MWCNT-COOH	19.7	31.4
5.5	Drug/MWCNT	58.3	73.8
	Drug/MWCNT-OH	67.1	82.4
	Drug/MWCNT-COOH	76.5	91.2

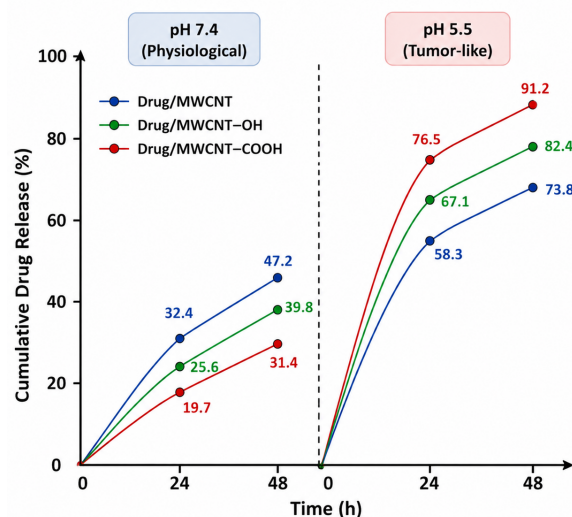


Figure 6: pH-responsive drug release behavior of functionalized MWCNT nanocarriers system

5. Discussion

The efficacy of MWCNTs as nanovehicles for anticancer drug transport is significantly enhanced by surface functionalization using -COOH and -OH functional groups. In comparison with pure CNTs, functionalized CNTs display improved properties in terms of adsorption capability, stability, and release control, based on the integrated findings obtained through DFT calculations, molecular dynamics, and MM/PBSA free energy studies.

Existing research in the arena of medication distribution systems using CNTs mostly deals with in

vitro performance and adsorption efficiency, with very limited in vivo testing and toxicity assessment [17-34]. Some of the articles fail to address the physiological variations and biodegradation in vivo in their study [20, 25, and 30]. Some other studies fail to perform adequate immune response and systemic safety tests [18, 22, and 32]. Moreover, the comparative analysis of the different functional groups (-COOH, -OH, etc.) in many of the studies is quite inconsistent, thus resulting in non-uniformity in adsorption efficiency [23, 28, 31]. The present research rectifies many of the limitations that exist in earlier research on the claim of CNTs in painkiller distribution through the integration of DFT, MD, and MM/PBSA approaches. The systematic evaluation of the pristine, -OH, and -COOH functionalized MWCNTs under similar conditions was evaluated in this research. The realistic analysis of controlled release, thermodynamic stability, and adsorption properties is achieved due to the inclusion of physiological and cancer-like pH in research.

The findings indicate the potential of functionalized MWCNTs as improved nanovehicles for targeted chemotherapeutic drugs through pH-sensitive release, higher drug loading, and better thermodynamic stability. This enables the development of safe and efficacious nanomedicine platforms for targeted therapy against cancer.

6. Conclusion

Some limitations of traditional CNT-driven medicine transfer systems include the inability to target accurately, instability in the adsorption of drugs, insensitivity to changes in pH levels, and lack of thermodynamic stability. In an attempt to increase adsorption efficiency and stability, and regulate the release of anticancer drugs, functionalized MWCNTs with -OH and -COOH were developed in research. MWCNT performance for drug delivery was greatly improved by functionalization. With the maximum charge transfer (0.196 e) and the smallest contact distance (2.34 Å), the COOH-modified CNT demonstrated the strongest adsorption (-67.25 kcal/mol). Superior stability was demonstrated by MD analysis (RMSD 0.26 nm, SASA 19.6 nm²). The highest favorable binding was found in MM/PBSA (-67.48 kJ/mol). At pH 5.5, pH-responsive release reached 91.2%, demonstrating effective tumor-targeted drug delivery behavior. The limitations of research include the lack of a toxicity profile, simplification of the CNT structure, and in silico simulation without the support of in vivo and scientific judgments. Future work needs will be conducted for targeted functionalization, experimental confirmation, and evaluation of drug delivery performance.

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