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An overview of theoretical investigations on interaction of drug molecule with functionalized carbon nanotubes as drug delivery system

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Abstract
CNTs are promising nano-carriers for both drugs as well as biomolecules. This study possesses in-depth knowledge and understanding of carbon nanotubes both for their pharmaco-toxicological properties in drug molecule, it is essential to recommended for routine clinical use in the form of drug delivery carriers in the diagnosis and treatments of many diseases. The surface modified or functionalized Carbon nanotubes (CNTs) can be used for different purposes like improving solubility, carrying various therapeutic, and targeting agents. The functionalization of CNTs can be done via covalent or noncovalent bonding. The Density functional theory calculations are very much helpful to understand the effects on covalently binding of drug molecule with functionalized carbon nanotubes and fullerenes. The present review focus on the structural stability of drug molecule and adsorption behaviour of molecules over various types of CNTs. In addition, progress in carbon nanotube technology may well lead to better insights into biological and physical chemistry processes through theoretical calculations. This will make it possible to find drug molecules more compatible with carbon nanotube to facilitate in medical field.

Keywords: Carbon nanotubes, drug molecule, density functional theory

1. Introduction
Nanotechnology is a wide area of research; it deals with a variety of materials produced at a nano-meter scale through different chemical and physical methods. The nanostructures can be used for application in targeted delivery of drugs and encapsulation of both hydrophobic and hydrophilic substances, drug stability is enhanced &provides site-specific delivery [1, 2].

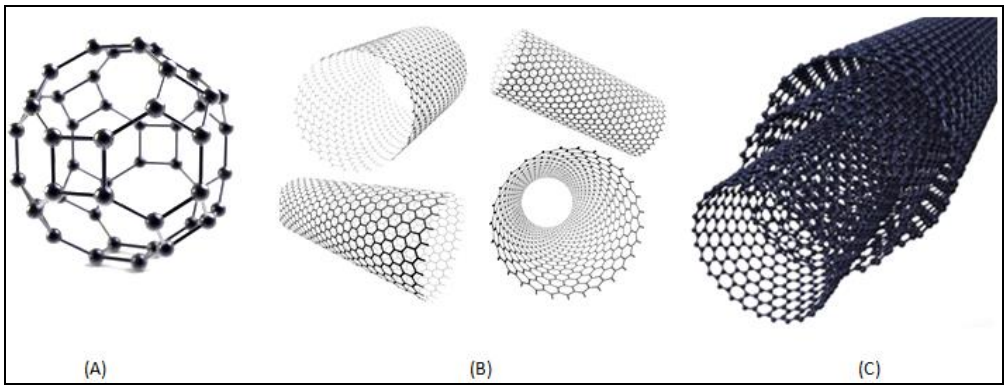

Fig 1: Classification of carbon nanotubes

Carbon nanotubes (CNTs) are tube-like materials, made up of carbon with a diameter on a nano-meter scale. Recently, CNTs have been widely used to deliver therapeutic agents to the targeted tissues and cells due to their physicochemical properties. The application of CNTs in various disciplines like nanotechnology, transistors, nanomedicine, biosensors, bioimaging, actuators, and condensers. CNTs can be classified into various types based the numbers of graphene sheets layered either single layered, multi layered or double layered as well as also as nanotubes based on chirality i.e. Single walled, multi walled, shown in Figure 1.

The good compatibility of CNTs functionalization helps to reduce systemic toxicity and improves the efficacy of therapeutic agent delivery. Carbon nanotubes are most exploited for various applications, which interacted with biomolecule, drug, and drug delivery to the targeted organs, biosensor diagnostic and analysis [3-5].

In this review, an overview of properties of carbon nanotubes on different clinical applications of CNTs such as disease diagnosis and drug targeting are discussed. The review mainly focusses on the basic structure of CNT, their functionalization, and interaction of drug and biomolecule nanocarrier system by means of density functional theory calculations.

2. Density functional theory Calculations

As a block diagram, the drug delivery mechanism is as shown in Figure 2.

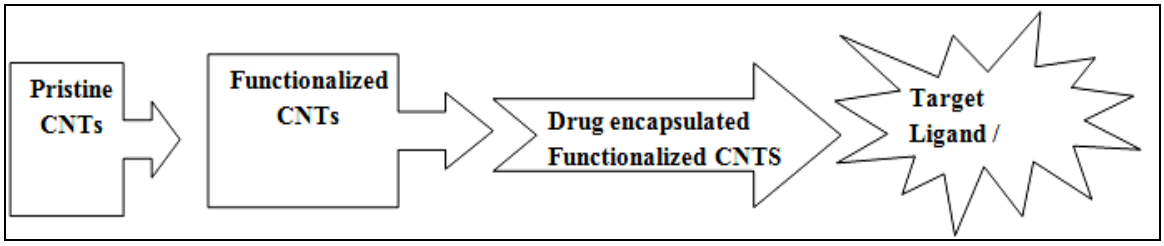

Fig 2: Drug Delivery Mechanism

Nagarajan *et al*. reported the first-principles studies on interaction of the flutamide (FLU) drug onto graphdiyne nanotube (Gdn-NT), and the favorable interaction sites of FLU on Gdn-NT, the results of the study recommend the use of Gdn-NT as a drug-delivery vehicle for FLU drug to the infected target cell, which is used to cure prostate cancer [6]. Based on DFT theory, the interaction and bond properties of anticancer drug doxorubicin (DOX), armchair single-walled carbon nanotube (SWCNT), and hydroxyl-and carboxyl-functionalized SWCNT (*f*-SWCNT) showed that hydrogen bonds between active sites of DOX molecules and hydroxyl- and carboxyl-functionalized CNTs played a more important role than those with pristine CNTs in the adsorption and fixation of the studied complexes as well as their thermodynamic energy [7]. The effect of ethanol as a co-solvent on the inclusion complex formation between Flutamide drug molecule and the carbon nanotube. The results reveals that the presence of ethanol at the concentration of 0.5 M enhances the stability of the simulation system. Taken altogether, the obtained data provide useful information about the ethanol co-solvent effects on the adsorption process [8].

Yoosefian *et al*. investigated the functionalized single-walled carbon nanotubes as a carrier for Droxidopa and observed more dispersibility of single-walled carbon nanotubes and improved bioavailability with reduced systemic toxicity [9]. The drug carrier, N-isopropyl acrylamide-Carbon nanotube is suitable for the delivery of Doxorubicin, and five mer N-isopropyl acrylamide is the optimum carrier for Doxorubicin loading [10]. The effect of the functional group of nano-carrier on the drug binding was investigated by all-atom molecular dynamics (MD) simulations of anticancer drug, paclitaxel (PTX), loaded with the pristine SWCNT and functionalized with (-OH), (-COOH), and PW3 peptide shows the biological applications of single-walled carbon nanotubes (SWCNTs) including biomolecules carriers [11].

Kamel *et al*. have studied the drug delivery performance of the functionalized (5, 5) single-walled carbon nanotube with a carboxylic acid group for Flutamide anticancer drug in the gas phase and water solution by means of density functional theory calculations and obtained that the drug molecules are strongly adsorbed on the functionalized nanotube surface [12]. The Density functional theory calculations on the effects of covalently binding isoniazid, an antitubercular compound to functionalized carbon nanotubes and fullerenes clearly shows the solubility of functionalized carbon nanotubes is higher than functionalized fullerenes and the dissolutions in water are thermodynamically favourable [13]. In a study, the drug loading efficacy of graphitic carbon nitride (g-C3N4) for an anticancer drug, cisplatin was evaluated, the findings suggest that g-C3N4 could be used as an efficient drug-delivery system for the cisplatin drug to treat various types of cancer [14].

Table 1: Few examples of CNTs as Drug Delivery carrier

S. No.	Drug carrier	Drug	Disease	Reference
1.	Graphdiyne nanotube (Gdn-NT)	Flutamide (FLU)	Cure prostate cancer	V. Nagarajan *et al.*
2.	Armchair single-walled carbon nanotube (SWCNT) and hydroxyl-and carboxyl-functionalized SWCNT (*f*-SWCNT)	Doxorubicin (DOX)	Anticancer drug	Sina Karimzadeh *et al.*
3.	Single-walled carbon nanotube	Flutamide	Anticancer drug	Maedeh Kamel *et al.*
4.	Single-walled carbon nanotubes	Droxidopa	Orthostatic hypotension	Mehdi Yoosefian *et al.*
5.	N-isopropyl acrylamide-Carbon nanotube	Doxorubicin	Anticancer drug	Reza Maleki *et al.*
6.	Single-walled carbon nanotubes (SWCNTs)	Paclitaxel (PTX)	Anticancer drug	Leila Tohidifar *et al.*
7.	Single-walled carbon nanotube	Flutamide	Anticancer drug	Maedeh Kamel *et al.*
8.	Carbon nanotubes and fullerenes	Antitubercular compounds	Tuberculosis	Marco Gallo *et al.*
9.	Graphitic carbon nitride	Cisplatin	Anticancer drug	Mehvish Perveen *et al.*
10.	Pristine and B-, Al-, Ga-doped C36 nanotube	Fluorouracil	Anticancer drug	Mustafa Kurban *et al.*
11.	Single-walled carbon nanotubes:	Carmustine	Brain tumors	Rabeeh Khorram *et al.*
12.	Functionalized carbon nanotube	2-methylheptylisonicotinate	Antitubercular drug	Nabanita Saikia,
13.	TiO_2 NT, SiO_2 NT and CNT	Chitosan monomer		
14.	Carbon nanotube	Hydroxyurea	Anti-cancer drug	Maryam Hesabi *et al.*
15.	Pristine, Al-, and Si-doped carbon nanotubes	5-fluorouracil	Cancer drug	Mohammad Yahyavi *et al.*

16.	Carbon nanotube	Cladribine	Anticancer drug	Mina Lotfi *et al.*
17.	Graphdiyne nanotube (Gdn-NT)	Imuran (Azathioprine) Pentasa (Mesalazine) Hyoscyamine (Daturine)	Crohn's disease and rheumatoid arthritis Crohn's and other inflammatory diseases Parkinson's disease symptoms	U. Srimathi *et al.*
18.	Carbon nanotubes (CNTs)	Efavirenz (EFV)	anti-HIV drug	Hong Xu *et al.*

Density functional theory (DFT) is used to examine the formation possibility of a stable interaction between 5-fluorouracil (5-FU) drug molecule and a pristine, boron (B), aluminum (Al) and gallium (Ga)-doped carbon nanotube (CNT), the observed result shows that Al-doped CNT has more desirable properties to use it as a drug delivery system [15]. The adsorption behavior of Carmustine drug on the surface of (5, 5) pristine single-walled carbon nanotube and the functionalized single-walled carbon nanotube with a carboxylic acid group is studied by density functional theory calculation, the result indicated that the Carmustine molecule can be adsorbed on the nanotube surface with a charge transfer from the nanotubes to drug molecule [16].

Carbon nanotubes can act as a suitable drug delivery vehicle for internalization of MHI within biological systems. The interaction of 2-methylheptylisonicotinate (MHI) drug with (5,5) armchair single-wall carbon nanotube (SWNT) of finite length is studied using density functional theory, the results are used to identify the potential applications of functionalized carbon nanotubes as drug delivery systems [17].

In a research work, theoretical studies on density functional theory (DFT) have performed to understand the interaction between the Chitosan (CS) monomer and three types of nanotubes, namely TiO2 nanotube (TiO2 NT), SiO2 nanotube (SiO2NT) and Carbon nanotube (CNT) [18].

The interaction of the anti-cancer drug hydroxyurea with carboxyl-functionalized zigzag carbon nanotubes (CNTs) studied by the method of the density functional theory (DFT) at B3LYP and CAM-B3LYP levels in gas and solvent phases, observed data indicates that adsorption is dependent on the carboxyl sites of the nanotube as well as on the sites of the drug, also the hydrogen-bonding interactions between drug and COOH-CNTs play an important role for the different kinds of adsorption observed [19].

Yahyavi *et al*. investigated the interaction between pristine and doped carbon nanotubes (CNTs), and 5-fluorouracil (5-FU) using density functional theory (DFT) method and suggest that Al-doped CNTs is expected to have promising application in the field of drug delivery [20]. Lotfi *et al*. studied the pristine (NT) and COOH (FNT) functionalized carbon nanotube, ten noncovalent configurations and four mechanisms of covalent functionalization of NT and FNT with cladribine anticancer drug (CDA), the free energies of solvation shows that NT and FNT solubility increases in all drug-nanotube configurations which is a main factor for its applicability in the drug delivery [21].

The density functional theory calculations of adsorption of the drugs, Imuran (Azathioprine), on graphdiyne suggested that the graphdiyne nanotube can be effectively utilized as a drug delivery system for the chronic disease drugs [22]. Xu *et al*. studied the capability of the boron nitride nanotubes (BNNTs) and carbon nanotubes (CNTs) as the delivery vehicles of EFV, the results suggested that EFV can be adsorbed physically on the CNTs with a stable state, indicating that CNTs may be a potential delivery vehicle of EFV, the computed interaction energies reveal that the adsorption of EFV on CNTs are more favorable than that on BNNTs [23].

3. Conclusion

CNTs are promising nano-carriers for both drugs as well as biomolecules. This study possess in-depth knowledge and understanding of carbon nanotubes both for their pharmaco-toxicological properties in drug molecule, it is essential to recommended for routine clinical use in the form of drug delivery carriers in the diagnosis and treatments of many diseases.

4. Future perspectives

The future research should be focus on investigating more efficient CNT based drug delivery for the betterment of human health. In addition, progress in carbon nanotube technology may well lead to better insights into biological and physical chemistry processes through theoretical calculations. This will make it possible to find drug molecules more compatible with carbon nanotube to facilitate in medical field.

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