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Quantum mechanical studies of the adsorption of Remdesivir, as an effective drug for treatment of COVID-19, on the surface of pristine, COOH-functionalized and S-, Si- and Al- doped carbon nanotubes

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ABSTRACT

Remdesivir has been recognized as an important medicine in the control of COVID-19 illness. Since carbon nanotubes were considered in the design of novel drug delivery vehicles, the interaction between simple CNT, functionalized CNT by carboxylic group and S-, Al-, and Si-doped CNT and Remdesivir drug were studied using density functional theory (DFT) and time dependent DFT (TDDFT) calculations. The results of this work show that the Si-doped CNT is the best drug delivery system for Remdesivir due to its better electronic, energetic, adsorption and thermodynamic properties.

1. Introduction

The new pandemic corona virus illness like SARS and MERS coronaviruses, has been called COVID-19 and recognized in Wuhan City of China, in December, 2019. Until November 2020, the World Health Organization (WHO) has reported more than 52 million cases of the virus and around 1,290,000 deaths, in entire of the world. It is noteworthy that older adults, especially those with earnest underlying health conditions, are at greater risk for intense COVID-19-related disease and death than are younger peoples. Also, the more percentage of deaths due to COVID-19, happened among peoples with aged 65 or over and the fewer percentage of death happened in persons with age 19 or smaller. The COVID-19 illness causes high mortality due to severe respiratory syndrome. Up till now, because of enhancement of coronavirus epidemic in entire of world, several clinical research groups are investigating the remedial choices for control of COVID-19 illness [1–6].

Different drugs were investigated for control of COVID-19 infection. Clinical researches show that Remdesivir (RDV, GS-5734) drug, which has been known as a promising antiviral drug against some RNA viruses, can be as an important drug in prophylactic and therapeutic efficacy of patients with COVID-19 illness. Remdesivir is a prodrug of a nucleoside analogue that hinders viral RNA polymerases because it is intracellularly metabolized to an analogue of adenosine triphosphate. The clinical and antiviral effectiveness of Remdesivir in COVID-19 illness remains to be

recognized [7–12]. In order to improve therapeutic efficiency of Remdesivir drug, the use of nano medicine and design of drug delivery vehicles based on nanomaterials, which may increase efficiency of absorption of drugs, is important [6,13].

Drug delivery systems have been recognized as one of the most significant topic in medical systems with the ability of increasing human health and employs nanomaterials to increase in vivo life time and the drug solubility [6,14–16]. Carbon based nanomaterials for example carbon nanotubes (CNTs), fullerene, graphene and boron nitride nanomaterials were extensively investigated in numerous applications for instance drug delivery systems as a consequence of their inimitable physical and chemical properties [17–24]. Carbon based nanomaterials can be categorized as smart materials because of their actuation properties, electrical conductivity, electrochemical sensing and high mechanical strength [6,25–27].

Among carbon based nanomaterials, carbon nanotubes (CNTs) because of their prominent chemical, electrical and mechanical properties such as high thermal, outstanding conductivity or semi-conductivity, small densities, chemical stability, tensile strength and surface topology have been widely used in various fields of nanotechnology applications such as catalysts, gas sensors, biosensors, nano-electronics, photo electronic devices, hydrogen storage devices in fuel cells, biology and medicine for in vitro and in vivo detection, imaging, carrier vaccine and drug delivery. Among several applications of CNTs,

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Fig. 1. Five different configurations for interaction between Remdesivir drug with the (5,5) SWCNTs optimized at the B3LYP/3-21G level.

Table 1

The energetic and thermodynamic parameters for five interaction configurations of Remdesivir with the CNT(5,5) optimized by B3LYP/3-21G method.

Configurations	E _{total} (Hartree)	E _{HOMO} (eV)	E _{LUMO} (eV)	E _g (eV)	E _{ads} (eV)	E + T (Hartree)	E + H (Hartree)	E + G (Hartree)
Configuration a	-6110.69	-4.36	-2.57	1.79	-0.22	-6109.1399	-6109.1327	-6109.3487
Configuration b	-6110.62	-4.46	-2.66	1.80	-0.18	-6109.1380	-6109.1301	-6109.3412
Configuration c	-6110.59	-4.42	-2.59	1.83	-0.12	-6109.1359	-6109.1343	-6109.3402
Configuration d	-6110.75	-4.50	-2.71	1.79v-0.28	-6109.1495	-6109.1476	-6109.3593	
Configuration e	-6110.71	-4.40	-2.58	1.82	-0.25	-6109.1418	-6109.1407	-6109.3559

the uses of carbon nanotubes as their exceptional role as carriers of drugs have been widely considered in the recent years [16,28–32]. One of the main limitations for the use of CNTs in drug delivery systems is the low

solubility and reactivity of CNTs in aqueous environment and organic media. In the direction of overcome these limitations and to increase their activities, modifications of CNTs by the covalent and non-covalent

Fig. 2. The optimized geometries of Remdesivir, CNT (5,5) and CNT(5,5)/Remdesivir (complex “d”) obtained with B3LYP/6-31G* method.

functionalization and also doping of various elements onto CNTs, can help them overcome these problems. The modified CNTs show various mechanical and physical properties relative to simple CNTs. Also, with the decrease in hydro-phobicity of surface and increase the mobility of CNTs, solubility improved and the damage to the live cells and toxicity have been decreased [16,28–35]. Chemical covalent functionalization of CNTs, which functional groups attach straight to the surface of CNTs through chemical reactions, is one of the best effective methods to improve their structures, chemical and electronic properties. The side-wall of CNTs functionalization shows the fewer damaging to the

surface of the CNTs and let the connection of various groups to connect by biomolecules. Oxidation through strong acid, among several types of functionalization of CNTs, is a public way. Carboxylation has been used to enhance the purification and dispersion of CNTs. Also, CNTs could be doped by various elements such as nitrogen, boron, sulfur, silicon and aluminum to improve their properties and have been extensively studied to develop good drug carriers. The S-, Si- and Al-Doped nanotubes have been extensively investigated for novel drug carriers. Therefore, because of the high adsorption strengths of functionalized CNTs and doped CNTs, they could be investigated as important nano carriers for the drug

Table 2

The adsorption energy and thermodynamic parameters of Remdesivir and CNT (5,5)/Remdesivir (complex “d”) optimized by B3LYP/6-31G* method in both gas and solvent phases.

	E_{ads} (eV)	$E + T$ (eV)	$E + H$ (eV)	$E + G$ (eV)
Configuration “d” (gas)	−0.719	−166242.27	−166242.24	−166248.07
Configuration “d” (water)	−0.924	−166243.06	−166242.98	−166249.11
Remdesivir (gas)	–	−62813.52	−62813.69	−62816.80
Remdesivir (water)	–	−63175.25	−63175.26	−63179.42

delivery of remedial molecules with better chemical adaptability [16,28,30,31,36–39]. Despite the noticeable benefits of expensive experimental ways, the computational studies with the purpose of the investigation of the mechanism of the interactions between drugs and CNTs, have been increasingly considered because of the expensive and time consuming of the empirical methods [6,14].

Several computational works were carried out in order to adsorption of some drugs on CNTs [16,28–32]. Since interaction between Remdesivir and CNTs have not been investigated computationally up to the present time, the interaction between simple CNT, functionalized CNT by carboxyl functional group and S-, Al- and Si-doped CNT and Remdesivir are studied on the basis of density functional theory (DFT) calculations to investigate the effects of carboxyl functional group and the dopant atoms on the CNT and the effects of Remdesivir adsorption on functionalized and doped CNTs. The energetic, electronic, absorption and thermodynamic properties, and also some quantum descriptors such as adsorption energy (E_{ads}), HOMO-LUMO energy difference (E_g), electrophilicity indexes (ω) and chemical hardness (η) were evaluated in the work.

2. Computational details

In this study, the interaction between Remdesivir drug and simple (5,5) armchair single-wall carbon nanotube (SWCNT), functionalized (5,5) armchair single-wall carbon nanotube by means of a carboxylic functional group and S-, Al- and Si-doped (5,5) armchair SWCNTs, were investigated by density functional theory (DFT) method. In order to estimate the energy of the most stable structure of CNT/Remdesivir complex, different configurations of Remdesivir and pristine CNT (5,5) were optimized in gas phase by the B3LYP/3-21G method. The most stable structure was optimized in both the gas phase and water phase with dielectric constant 78.4 through the conductor polarizable continuum model (CPCM) [40–42] through B3LYP functional and 6-31G* basis set, using Gaussian 09 program [43], with the aim of investigation of the solvent effects on the electronic properties and stabilities of CNT/Remdesivir complex. Solvation energies ($E_{\text{solv}} = E_{\text{sol}} - E_{\text{gas}}$) have been calculated from the difference between the total energy of the molecule in the solvent phase and the total energy of the molecule in the gas phase [6,13,14,31]. Frequency calculations were performed on the

Table 3

Energetic parameters and electronic properties of Remdesivir, CNT(5,5) and the most stable configuration of CNT/Remdesivir in the gas phase and water media at the B3LYP/6-31G* level of theory.

Structure	E_{HOMO} (eV)	E_{LUMO} (eV)	E_g (eV)	ΔE_g (%)	η (eV)	ω (eV)	ECT	μ_D (Debye)	E_{ads} (kcal/ mol)	E_{sol} (kcal/ mol)	ΔG (kcal/ mol)	ΔH (kcal/ mol)
gas												
Remdesivir	−5.92	−1.00	4.92	–	2.46	2.43	−5.	–	–	–	–	–
CNT(5,5)	−4.61	−2.82	1.79	–	0.89	7.73	–	0.0	–	–	–	–
Complex “d”	−4.60	−2.81	1.78	0.15	0.89	7.70	−2.74	5.96	−16.580	–	–	–
water												
Remdesivir	−6.41	−1.55	4.86	–	2.43	3.26	–	8.46	–	−28.60	–	–
CNT(5,5)	−4.87	−3.07	1.79	–	0.89	8.77	–	0.0	–	−14.632	–	–
Complex “d”	−4.91	−3.13	1.78	0.18	0.89	8.98	−2.83	8.85	−21.307	−30.659	−1.65	−15.19

optimized structures at the same level of theory.

Adsorption energies (E_{ads}), that show relative stability of the carbon nanotube–drug complexes, can be calculated through Eq. (1).

$$E_{\text{ads}} = E_{\text{complex}} - [(E_{\text{CNT or fCNT or dopedCNT}}) + E_{\text{drug}}] + E_{\text{BSSE}} \quad (1)$$

Where, E_{complex} is the total energy of the CNT or fCNT or dopedCNT/drug complexes after geometry optimization. E_{CNT} , E_{fCNT} , E_{dopedCNT} and E_{drug} are the energies of the pristine CNT, functionalized CNT, doped CNTs and drug, respectively [13,14]. The basis set superposition errors energy (BSSE) corrections using the counterpoise (cp) correction, were used to correct the adsorption energies [30,44,45]. The considered structures with charge $Q = 0$ are neutral and have been stabilized by multiplicity $M = 2S + 1$, where S is the total spin of one [6,21,22].

The electronic properties and the quantum molecular descriptors such as the highest occupied molecular orbital (E_{HOMO}), the lowest unoccupied molecular orbital (E_{LUMO}), energy gap between LUMO and HOMO ($E_g = E_{\text{LUMO}} - E_{\text{HOMO}}$), the chemical potential (μ) which determines the evasion affinity of a molecule from equilibrium, chemical hardness (η) which measures the charge transfer and the chemical reactivity of a molecule, electronegativity (χ) which identify the power of a molecule to attract electrons and electrophilicity index (ω) as a parameter that greater value of ω means higher electrophilic power of a molecule, were calculated by means of the following equations which each parameter can be obtained from DFT optimization calculations [13, 14]:

$$\mu = (E_{\text{HOMO}} + E_{\text{LUMO}})/2 \quad (2)$$

$$\eta = [-E_{\text{HOMO}} - (-E_{\text{LUMO}})]/2 \quad (3)$$

$$\chi = -(E_{\text{HOMO}} + E_{\text{LUMO}})/2 \quad (4)$$

$$\omega = \chi^2 / 2\eta \quad (5)$$

The maximum electronic charge ΔN_{max} of a molecule which can receive from the environment could be obtained with Eq. (6) [6,13,46]:

$$\Delta N_{\text{max}} = \mu / \eta \quad (6)$$

Hence, electrophilicity index, can be written on the basis of ΔN_{max} as Eq. (7):

$$\omega = \mu^2 / 2\eta = (-\mu / \eta) \chi \Delta N_{\text{max}} / 2 \quad (7)$$

So, the maximum electronic charge ΔN_{max} can be calculated on the basis of electronegativity (χ) and electrophilicity index (ω) as the following equation:

$$\Delta N_{\text{max}} = 2\omega / \chi \quad (8)$$

Consequently, the amount of charge transfer between two molecules, such as one drug and CNT, could be calculated by electrophilicity index and is known as electrophilicity-based charge transfer (ECT) and was obtained with Eq. (9):

$$ECT = (\Delta N_{\text{max}})A - (\Delta N_{\text{max}})B = 2[\omega_A X_A - \omega_B X_B] \quad (9)$$

Fig. 3. Calculated HOMO and LUMO orbitals of Remdesivir, CNT(5,5) and the most stable structure of CNT(5,5)/Remdesivir complex.

On the basis of Eq. (9), If $ECT < 0$, A is an electron donor and if $ECT > 0$, A is an electron acceptor [6,13,46].

Also, natural population analysis (NPA) and molecular electrostatic potential (MEP) have been analyzed with the aim of consideration of the charge distributions and better insight of the interactions. As well as, time-dependent DFT (TDDFT) calculations have been carried out by the similar procedure in order to investigation of the electronic absorption spectra of the studied compounds.

3. Results and discussion

3.1. Optimized structures and electronic properties

Five different geometric configurations for interaction between

Remdesivir drug with the (5,5) SWCNTs have been optimized at the B3LYP/3-21G level to find the most stable structure for interaction between Remdesivir and the CNT. The optimized structures of the five different configurations by B3LYP/3-21G method, have been shown in Fig. 1.

According to the results of Table 1, the obtained values of energy (E) and also thermodynamic quantities such as (E + T), (E + H) and (E + G) that means the sum of electronic and thermal energies, the sum of electronic and thermal enthalpies and the sum of electronic and thermal free energies, respectively, for the five configurations ("a", "b", "c", "d" and "e") of the Remdesivir with the CNT (5,5) optimized by B3LYP/3-21G method show that configuration "d" has the lowest energy values.

Moreover, the calculated adsorption energies between the CNT and different configurations of Remdesivir at the B3LYP/3-21G level which

Fig. 4. Molecular electrostatic potential (MEP) surfaces of Remdesivir, CNT(5,5) and the most stable structure of CNT(5,5)/Remdesivir complex calculated using the B3LYP/6-31G* method.

are listed in Table 1, show that configuration "d" has the most negative adsorption energy. On the basis of the above results, configuration "d" is the best possible configuration for interaction between Remdesivir and the CNT and is the most stable structure among the other structures.

Thus, in the following, the most stable structure (configuration "d") has been optimized by B3LYP/6-31G* method in both gas and solvent phases. The optimized geometries of Remdesivir, CNT (5,5) and CNT/Remdesivir complex obtained with B3LYP/6-31G* have been shown in Fig. 2. The calculated adsorption energies with BSSE corrections of the

most stable structure of CNT/Remdesivir complex, shown in Table 2, was obtained -0.719 and -0.924 eV in the gas phase and water solvent, respectively. The adsorption energy in the solvent is more negative than in the gas phase. Also, the negative values of adsorption energies show that these reactions are exothermic. The small adsorption energies specified that the interaction between the simple CNT and Remdesivir typically occurs through noncovalent interaction and this indicates that there is a physisorption between the CNT and Remdesivir [13,14].

Also, thermochemical quantities for the most stable structure of CNT

Table 4

The values of natural atomic charges of some atoms with more negative and more positive charges of the functionalized and doped CNT(5,5) complexes with Remdesivir calculated with B3LYP/6-31G* method.

Atom	Remdesivir	Atom	fCNT Drug	Atom	S-dopedCNT Drug	Atom	Si-dopedCNTDrug	Atom	Al-dopedCNT Drug
P 1	2.12195	C 14	-0.21091	C 14	-0.22590	C 14	-0.22408	C 14	-0.21187
O 3	-0.67528	C 91	-0.22046	C 50	-0.35499	C 50	-0.59050	C 50	-0.68089
O 5	-0.72201	C 121	0.82665	P 120	2.14681	C 87	-0.23806	C 51	-0.64146
O 6	-0.70787	O 122	-0.60526	O 126	-0.90427	P 120	2.14310	C 69	-0.63091
O 7	-0.86042	O 123	-0.57171	N 131	-0.99968	O 126	-0.90150	P 120	2.14280
N 12	-1.00508	H 124	0.48727	N 134	-0.77278	N 131	-0.99683	O 124	-0.71718
N 15	-0.77421	P 125	2.14246	C 144	-0.29215	N 134	-0.76998	O 126	-0.90152
C 33	0.74408	O 128	-0.71039	C 145	0.43279	C 141	0.50502	N 131	-0.99551
C 34	-0.69223	O 131	-0.90141	C 153	-0.69088	C 152	0.75827	N 134	-0.77362
H 48	0.44573	N 136	-0.99626	C 155	-0.69734	C 155	-0.69768	C 152	0.76353
H 50	0.45719	N 139	-0.77375	H 167	0.45252	H 167	0.46274	C 155	-0.69759
H 52	0.43281	H 174	0.48215	H 169	0.46689	H 169	0.49215	H 169	0.46673
H 62	0.41222	H 172	0.44635	H 171	0.43180	H 171	0.43687	H 171	0.43223
H 63	0.42149	H 176	0.43052	S 197	0.90334	Si 197	1.77319	Al 197	1.53682

(5,5)/Remdesivir complex and Remdesivir using B3LYP/6-31G* method, are shown in Table 2. On the basis of the obtained results, when Remdesivir is in physisorption interaction with the CNT(5,5), the Enthalpy and Gibbs energies values reduce. The values of energy indicate the increase stability and reduced reactivity of the Remdesivir in the presence of CNT(5,5).

The electronic properties obtained in both gas and water phases and also solvation energies (E_{sol}) for Remdesivir, CNT(5,5) and the most stable configuration of CNT(5,5)/Remdesivir complex, are shown in Table 3.

The obtained values of E_{HOMO} , E_{LUMO} and HLG ($E_{\text{LUMO}} - E_{\text{HOMO}}$) of the investigated structures indicate that the HOMO and LUMO energies of all the compounds in water are more negative relative to the gas phase. The HLG value of Remdesivir in water is lesser than that of this drug in the gas phase. It is concluded that the adsorption of Remdesivir on pristine CNT, do not change the values of HLG (E_{g}), obviously. Therefore, the E_{g} of CNT(5,5) through interaction by Remdesivir in configuration “d” changed fewer and therefore we can conclude that this compound is an electronically innocuous interaction and the nano-carrier would not alter the medicine properties, significantly [14]. With the purpose of investigation of the electronic sensitivity and to associate E_{g} energy to the electrical conductivity, the next equation was usually applied:

$$\sigma \propto \exp(-E_{\text{g}} / 2kT) \quad (10)$$

According to this equation, the electrical conductivity has an exponential relation with E_{g} energy, where in the formula, k is the Boltzmann's constant [13]. The ΔE_{g} values reported in Table 3 show that the conductivity of the complex “d” enhanced in water media relative to the gas phase.

The frontier molecular orbital (FMO) of Remdesivir, CNT(5,5) and the most stable structure of CNT(5,5)/Remdesivir have been shown in Fig. 3. The frontier molecular orbital (FMO) analysis of Remdesivir displays that the HOMO orbital of this molecule largely focuses on double bonds (-C=C-), (-C=N-) and (-N=N-) of aryl ring, while the LUMO orbital are located on double bonds (-C=C-), (-C=N-) and (-N=N-) of aryl ring and slightly on C16-C22 and C22 = N13 bonds and oxygen atom. In the CNT(5,5), the HOMO and LUMO orbitals mostly located on double bonds (-C=C-). The E_{g} of the CNT(5,5) in the gas phase is 1.79 eV and after adsorption of the Remdesivir on CNT(5,5) it is reduced to 1.78 eV. Also, FMO analysis of the CNT(5,5)/Remdesivir show that the HOMO and LUMO orbitals are located on double bonds (-C=C-) of CNT.

Moreover, the values of electrophilicity index and chemical hardness reported in Table 3 that can be used to estimate the reactivity and chemical stability of molecules [13], display that chemical hardness value of complex “d” has not been changed from gas phase to solvent phase while electrophilicity indexes of the complex enhances in solvent.

Enhancement of electrophilicity index of this configuration relative to the Remdesivir and CNT(5,5), means that interaction of the medicine with the CNT created better electrophilic characteristic for the investigated complex [14].

The values of dipole moment in water solvent are greater than those of in the gas phase. The dipole moments of CNT(5,5) ($\mu = 0$) increase significantly after interaction with the drug as a result of the perturbation in the electron density. It is significant that the dipole moment of complex “d” is slightly higher than that of the single drug in the both media which shows that adsorption of Remdesivir on the CNT(5,5) enhances the polarity of the system that is a good feature for drug delivery in biological environments [44].

The negative values of ECT of the most stable structure of CNT/Remdesivir complex in both gas and solvent phase, display that Remdesivir drug is an electron donor and the CNT is an electron acceptor and therefor charge release from Remdesivir to the CNT. Also, the absolute value of ECT in the solvent phase is slightly higher than that of in the gas phase, which shows that the interaction in the solvent phase is better relative to the gas phase.

The negative values of the solvation energy display that the molecules are stable in water solvent. When the degree of solubility is higher, the more negative solvation energy has been obtained [6,14]. The calculated solvation energies indicate that the complex are stabilized in the presence of water. Therefore, the solubility of this complex can be improved when the medicine are adsorbed on the CNT(5,5) surface in water.

According to the above results, it is concluded that complex “d” which can be selected as the most stable configuration among the other configurations, is the best configuration to study the effect of doped CNT (5,5) with S, Si and Al dopant atoms and functionalized CNT(5,5) with carboxylic group on the adsorption behavior of Remdesivir.

3.2. Molecular electrostatic potential (MEP) and NPA analysis

Molecular electrostatic potential (MEP) map that displays the electronic density in the molecules, is a suitable descriptor to identify the best site of interaction for the donor-acceptor complexes and to recognize sites of positive and negative electrostatic potentials for nucleophilic reactions and electrophilic attack. The negative regions of electrostatic potential with the high electron density which are specified by red, orange and yellow color, have been associated to electrophilic reactivity. But, the positive regions of electrostatic potential with the low electron density that are shown with blue color, have been associated to nucleophilic reactivity and green color of MEP identifies the neutral regions [29,30]. MEP plot of Remdesivir, CNT(5,5) and the most stable configuration of CNT/Remdesivir complex have been shown in Fig. 4. The MEP maps of Fig. 4 and the natural atomic charges values of some atoms with more positive and more negative charges that are

Fig. 5. Molecular electrostatic potential (MEP) surfaces of doped and functionalized CNT(5,5) complexes with Remdesivir calculated using the B3LYP/6-31G* method.

gathered in Table 4, display that the negative sites of Remdesivir are placed on the O atoms and N atoms specially the most negative site has been observed in O8 and N12 atoms which are connected to P atom, and the positive sites are placed on hydrogen atoms, specially the hydrogen atoms of $-NH_2$, $-NH$ and $-OH$ groups. The negative sites of the nanotube are located over the simple carbon nanotube which has been shown with

orange color and the positive site of the nanotube is focused on terminal hydrogen bond which has been shown with blue color. In the CNT/Remdesivir complex, the region with red and yellow colors have the highest electron density and the region with the blue color have electropositive atoms. Also, the green color shows the neutral part of the CNT(5,5)/Remdesivir complex.

Fig. 5. (continued).

Fig. 6. The optimized structures of complexes between Remdesivir and doped and functionalized CNT(5,5) by B3LYP/6-31G* method.

With the intention of study the adsorption behavior of Remdesivir on functionalized and doped CNT by carboxyl functional group and S, Si and Al dopant atoms, the values of natural atomic charges for the S-, Al-,

and Si-doped CNTs and the COOH-functionalized CNT complexes with Remdesivir computed with B3LYP/6-31G* method as well as MEP maps of these complexes were obtained. The values of Table 4, display that in

Table 5

Energetic parameters and electronic properties of the COOH-functionalized CNT(5,5) and S-, Si- and Al-doped CNT(5,5) with Remdesivir at the most stable structure in water media.

Structure	E _{HOMO} (eV)	E _{LUMO} (eV)	E _g (eV)	η (eV)	ω (eV)	ECT	μ_D (Debye)	E _{ads} (kcal/ mol)	E _{solv} (kcal/ mol)	ΔG (kcal/ mol)	ΔH (kcal/ mol)
COOH-CNT Remdesivir	-4.90	-1.25	3.64	1.82	2.59	-0.27	6.31	-21.63	-27.34	-6.50	-29.15
S-doped CNT Remdesivir	-4.42	-2.70	1.71	0.85	7.38	-2.73	7.11	-22.13	-30.01	-7.64	-32.09
Si-doped CNT Remdesivir	-4.10	-2.45	1.65	0.82	6.50	-2.55	12.94	-29.39	-36.62	-10.87	-38.65
Al-doped CNT Remdesivir	-4.75	-1.42	3.32	1.66	2.85	-0.44	7.94	-21.90	-28.06	-6.86	-29.89

all the structures, the O atoms and the N atom of the Remdesivir which is linked to the P atom shows the higher negative atomic charges, specially the N atom has the most negative atomic charges among the other atoms. Also, the P, S, Si, and Al atoms have the highest positive atomic charges. Besides, the H atoms which are connected to O and N atoms with more negative atomic charges, show more positive charges. In the COOH functionalized CNT/Remdesivir complex, the H atom of COOH group and the H atom which is linked to O128 shows the most positive atomic charge relative to the other H atoms. In S-, Si- and Al-doped CNT/Remdesivir complexes, H169 shows the highest positive atomic charge among the other H atoms. Among S, Si and Al atoms in all the complexes, the Si atom in the Si-doped CNT/Remdesivir complex has the highest positive atomic charges.

Also, according to the MEP maps of the functionalized and doped CNT complexes (Fig. 5), the active sites for doped CNT complexes are S, Si and Al atoms because of the positive charge distribution nearby the dopant atoms that are presented with blue/green color. Consistent with Fig. 5, the color code of COOH-, S-, Si-, and Al-doped CNT complexes are between $-7.290e^{-2}$ and $+7.290e^{-2}$; $-7.324e^{-2}$ and $+7.324e^{-2}$; $-8.320e^{-2}$ and $+8.320e^{-2}$; and $-7.120e^{-2}$ and $+7.120e^{-2}$, respectively. These data display that the electrostatic potential value of the Si-doped CNT/Remdesivir complex is higher than that of the other structures.

3.3. Adsorption of Remdesivir on functionalized and doped CNT(5,5)

Since chemical functionalization of CNT by carboxyl functional group and dopant atoms improve their solubility in water, one of carbon atoms on CNT(5,5) in compound “d”, is linked to the carboxyl functional group and has been replaced by the S, Si and Al dopant atoms and the obtained structures have been optimized using the B3LYP/6-31G* method. Because of the positive charge on these dopant atoms, the active sites of the doped CNT complexes, are S, Si and Al atoms. The optimized geometries of the studied complexes were presented in Fig. 6. To consider deformations at the place where the dopant atoms were doped in the CNT (5,5), for complex “d”, the distance between the C51 atom of simple CNT in the hexagonal ring and N133 atom of Remdesivir has been obtained 3.57 Å. When the carbon is replaced by S, Si and Al, the distance between the dopant atoms and the N132 atom of Remdesivir, were reduced and reported as 2.90, 1.98 and 2.79 Å, respectively. Also, the distance between the O atom of COOH group of the functionalized CNT and the N137 atom of Remdesivir was reported as 2.98 Å. The results demonstrate that the deformation because of Si dopant atom and the decrease of the distance between the dopant atom and the N atom of Remdesivir in the Si-doped CNT complex is more noticeable compared to the other complexes that show that the interaction between the Si-doped CNT and Remdesivir is relatively better than the other complexes which can be associated to the relatively larger size and higher positive charge of Si atom.

The values of electronic properties and adsorption energies of the functionalized and doped CNT(5,5) complexes with Remdesivir, calculated in the solvent, were listed in Table 5.

The negative values of adsorption energies (E_{ads}) for all these

complexes, show that the interaction of Remdesivir with functionalized and doped CNTs are exothermic interactions and the amount of these values and the value of adsorption energy of Remdesivir on piristin CNT (Table 3) indicate that the interaction between the doped and functionalized CNTs and Remdesivir are stronger than the interaction between the pristine CNT and Remdesivir because of the higher absolute values of adsorption energies of the functionalized and doped CNTs with Remdesivir. The adsorption energy (E_{ads}) of the Si-doped CNT/Remdesivir complex is more negative compared to the other complexes that shows stronger interaction between the Si-doped CNT and Remdesivir relative to the other functionalized and doped CNTs and this drug. The COOH-functionalized CNT/Remdesivir and Al-doped CNT/Remdesivir complexes, have smaller adsorption energies that means the weaker interaction of Remdesivir with these structures. We can conclude that the COOH group which shows the smallest deformations relative to the other dopant atoms placed in the CNT, shows the smallest adsorption energy in magnitude and the weakest interaction with Remdesivir.

The order of solubility of these compounds, according to the solvation energies obtained in water solvent, is as: Si-doped CNT/Remdesivir > S-doped CNT/Remdesivir > Al-doped CNT/Remdesivir > COOH-functionalized CNT/Remdesivir. The largest and smallest absolute value of solvation energies were observed for the Si-doped CNT/Remdesivir and the COOH-functionalized CNT/Remdesivir, respectively. Comparing solvation energies of simple CNT complex with Remdesivir and functionalized and doped CNTs complexes with Remdesivir display that the functionalization of the CNT by COOH group and dopant atoms improve the solubility.

For the Al-doped CNT and COOH-functionalized CNT complexes, Singly Occupied Molecular Orbital (SOMO) was demonstrated as the HOMO and E_g is defined as LUMO- SOMO energy gap. Because S, Si and carbon atoms have the similar number of valence electrons, doping of CNT with S and Si does not change the net occupancy of the energy levels relative to Al dopant and COOH group [14]. The E_g reported in Tables 3 and 5 indicate that doping S and Si atoms in the CNT reduces the energy gap (E_g) of the doped compounds compared to the simple CNT/Remdesivir complex “d” and the amount of this decrease for the Si-doped CNT/Remdesivir complex is higher than the S-doped CNT/Remdesivir complex. It can be concluded that Si atom because of its higher positive natural atomic charge and its relatively larger size compared to the other dopants has a greater effect on decreases of E_g of this complex.

Also, the decrease of E_g for the S- and Si-doped CNT/Remdesivir complexes relative to the pristine CNT/Remdesivir (complex “d”) shows that the conductivities of these complexes have been increased compared to the complex “d”. Specially, the conductivity of the Si-doped CNT/Remdesivir complex is higher because of the higher decrease of E_g value that is agreement with the better reactivity of this compound. Since the E_g has been recognized as a parameter for kinetic stability and reactivity [13], the smallest value of E_g of the Si-doped CNT/Remdesivir complex and its smallest chemical hardness means higher reactivity of this complex relative to the other structures.

In addition, the values of ω and ECT of these structures show that the amount of these parameters for the Si-doped CNT/Remdesivir and S-

Fig. 7. IR spectra for a) Remdesivir, b) Complex “d” (CNT/Remdesivir), c) S-doped CNT/Remdesivir, d) Si-doped CNT/Remdesivir, e) Al-doped CNT/Remdesivir, f) COOH-functionalized CNT/Remdesivir.

doped CNT/Remdesivir complexes are higher than these values for the Al-doped CNT/Remdesivir and COOH-functionalized CNT/Remdesivir complexes, which the results are consistent with the results of E_g , adsorption energies, chemical hardness and solvation energies of the structures.

By substituting one C atom of the CNT by the dopant atoms and COOH functional group, the electron density has been perturbed and the values of dipole moments enhance by doping with the dopants. The results of dipole moments (Table 5) and natural charges (Table 4) of these complexes show that the order of dipole moments is correlated to

the positive natural charges of the dopant atoms. The Si atom is the most electropositive compared to the other dopants, loses more charges to the CNT. So, it achieves more positive charges and therefore the dipole moments of this structure is greater than the other structures. Since dipole moment is related to the amount of the charges along with separation between them [47], the Si atom in the Si-doped CNT/Remdesivir complex with the largest dipole moment, displays the highest positive charge relative to the positive charges of S and Al dopants in their complexes.

So, it can be concluded that the dopant atoms and COOH group

Table 6

Calculated excitation energies (eV)/maximum wavelengths ($\lambda_{\max}$) (nm), oscillator strengths (f) and configurations composition of Remdesivir, the most stable structure of CNT/Remdesivir (complex "d") and the functionalized and doped CNTs complexes with Remdesivir calculated with TDDFT-B3LYP/6-31G*.

Compound	Excitation energies (eV)/ $\lambda_{\max}$ (nm)	f	Configurations Composition
Remdesivir	5.45/227.46	0.3353	0.37 (H $\rightarrow$ L+1)+ 0.17 (H-6 $\rightarrow$ L)+ 0.33 (H-3 $\rightarrow$ L)+0.25 (H-2 $\rightarrow$ L)+ 0.11 (H $\rightarrow$ L+3)+0.27 (H $\rightarrow$ L+5)
Remdesivir/ CNT (d)	2.17/570.35	0.7006	0.49 (H-1 $\rightarrow$ L)+ 0.48 (H $\rightarrow$ L+1)
COOH-CNT/ Remdesivir	2.07/596.46	0.1469	0.18 (H-3 $\rightarrow$ L)+0.36 (H-2 $\rightarrow$ L)+ 0.19(H-2 $\rightarrow$ L+1)+ 0.14(H-1 $\rightarrow$ L)+0.39 (H-1 $\rightarrow$ L+1) +0.13 (H $\rightarrow$ L+3)+0.18(H $\rightarrow$ L+1) +0.12 (H $\rightarrow$ L+3)+ 0.15 (H $\rightarrow$ L+4)+ 0.33 (H-2 $\rightarrow$ L) +0.27 (H-2 $\rightarrow$ L+1) +0.44 (H-1 $\rightarrow$ L+1)
S-doped CNT/ Remdesivir	2.15/574.29	0.1618	0.31 (H-2 $\rightarrow$ L)+ 0.18 (H-2 $\rightarrow$ L+1)+0.18 (H-1 $\rightarrow$ L)+0.25 (H-1 $\rightarrow$ L+1)+0.13 (H $\rightarrow$ L+1) +0.22 (H $\rightarrow$ L+3)+0.40 (H $\rightarrow$ L+4)
Si-doped CNT/ Remdesivir	2.04/606.63	0.2337	0.43 (H-1 $\rightarrow$ L+1)+ 0.26 (H-2 $\rightarrow$ L)+0.34 (H-1 $\rightarrow$ L)+0.12 (H-1 $\rightarrow$ L+2)+0.16 (H $\rightarrow$ L+1) +0.18 (H $\rightarrow$ L+2) +0.14 (H $\rightarrow$ L+4)
Al-doped CNT/ Remdesivir	2.06/600.04	0.1503	0.25 (H-2 $\rightarrow$ L)+0.28 (H-2 $\rightarrow$ L+1)+ 0.16(H-1 $\rightarrow$ L) +0.31 (H-1 $\rightarrow$ L+1)+0.17 (H-1 $\rightarrow$ L+3) +0.14 (H $\rightarrow$ L+1) +0.11(H $\rightarrow$ L+4) +0.14 (H $\rightarrow$ L+5) +0.20 (H-2 $\rightarrow$ L)+ 0.12 (H-1 $\rightarrow$ L) +0.52 (H-1 $\rightarrow$ L+1)

inserted in the CNT, enhance the electronic properties of the CNT in interaction with the drug. Among S, Si and Al dopant atoms, Si dopant shows higher effects on electronic properties of the CNT.

Moreover, the thermodynamic probability of Remdesivir adsorption on the pristine CNT and the doped and functionalize CNTs have been studied by calculation of the Gibbs free energy changes (ΔG) and the enthalpy changes (ΔH) at $P = 1$ atm and $T = 298.14$ K which were computed by the results of vibrational frequency calculations and are listed in Tables 3 and 5. The negative values of ΔG and ΔH display that

all these adsorptions are exothermic. These values show that the order of enthalpy changes and Gibbs free energy are comparable to the order of the adsorption energies of these complexes. The Si-doped CNT/Remdesivir compound show the most negative ΔG and ΔH , similar to the results of the E_{ads} . The more absolute values of ΔH relative to ΔG can be associated to the entropic effect. The absolute values of ΔH and ΔG for Remdesivir adsorption on the simple CNT are smaller than those of Remdesivir adsorption on the functionalized and doped CNTs. It demonstrates that the adsorption of Remdesivir on the functionalized and doped CNTs, with more negative values of ΔH and ΔG , especially adsorption of Remdesivir on the Si-doped CNT is more desirable, thermodynamically.

3.4. Vibrational properties

The infrared (IR) spectra of Remdesivir and the most stable configuration of CNT/Remdesivir complex, and the functionalized and doped CNTs, which were calculated from frequency calculations, were shown in Fig. 7. No imaginary vibrational modes have been observed for all the structures that confirms the geometrical stability of all the compounds. The IR spectra of Remdesivir indicates that the frequencies of the strongest IR bands of Remdesivir has been observed in the 1217 cm^{-1} which has been associated to the C33-O8 stretching modes of Remdesivir. The IR spectra of the CNT/Remdesivir complex displays that the frequencies of two strongest IR bands were observed at 1170 cm^{-1} and 3519 cm^{-1} that has been associated to the C147-N132 and P121-O127 stretching modes and N137-H172 stretching mode of the complex, respectively. Fig. 7 show that after Remdesivir adsorption on the CNT (5,5), the IR spectra has not been changed noticeably. But the intensity of IR bonds of CNT/Remdesivir complex are relatively higher than single Remdesivir. The IR spectra of Remdesivir complexes with the functionalized and doped CNTs show that the frequencies of the two strongest IR bands of the S-doped CNT/Remdesivir; Si-doped CNT/Remdesivir; Al-doped CNT/Remdesivir and COOH-functionalized CNT/Remdesivir complexes have been observed at the 1169 and 3132 cm^{-1} ; 1682 , 3584 cm^{-1} ; 1536 and 3062 cm^{-1} and 1536 and 3513 cm^{-1} , respectively. It is concluded that the strongest IR bands of the Si-doped CNT/Remdesivir complex have higher frequencies compared to the other complexes.

Fig. 8. UV-Vis spectra of Remdesivir, Complex "d" (CNT/Remdesivir), S-, Si-, Al- doped CNT/Remdesivir and COOH-functionalized CNT/Remdesivir complexes.

Fig. 9. The frontier molecular orbitals related to the main transitions of all the investigated structures.

3.5. Electronic structure and excited states

The calculated electronic absorption spectra of the optimized structures of Remdesivir, the most stable structure of CNT/Remdesivir (configuration "d") and the functionalized and doped CNTs complexes with Remdesivir, were calculated using time dependent DFT (TDDFT) method with B3LYP/6-31G* method. The excitation energies, maximum wavelengths ($\lambda_{\max}$), oscillator strengths (f) and configurations composition of these structures have been listed in Table 6. Besides, the calculated electronic absorption spectra of these structures have been shown in Fig. 8.

According to the results of Table 6 and Fig. 8, electronic absorption

spectra of Remdesivir shows that the strongest absorption peak is observed at $\lambda_{\max} = 227.46$ nm with oscillator strength $f = 0.3353$. This maximum wavelength is because of charge transfer of electron into the excited state $S_0 \rightarrow S_{10}$ and correlated to six configurations for electron excitations [(H $\rightarrow$ L+1), (H-6 $\rightarrow$ L), (H-3 $\rightarrow$ L), (H-2 $\rightarrow$ L), (H $\rightarrow$ L+3), (H $\rightarrow$ L+5)], which the (H $\rightarrow$ L+1) transition is the main transition associated to this maximum wavelength. The shape of the frontier molecular orbitals related to the main transitions of all these structures, are presented in Fig. 9. According to Fig. 9, because the frontier molecular orbitals are largely composed of pi (π) atomic orbitals, therefore the main electronic transition of Remdesivir corresponds to $\pi \rightarrow \pi^*$ transitions.

Fig. 9. (continued).

Besides, the strongest absorption band in electronic absorption spectra of the CNT/Remdesivir (complex “d”) is observed at $\lambda_{\max} = 574.29$ nm with the oscillator strength $f = 0.70$ which this peak has been associated to the charge transfer of electron into the excited state $S_0 \rightarrow S_4$ and is related to two configurations for excitations $[(H-1 \rightarrow L), (H \rightarrow L+1)]$, with relatively similar compositions. On the basis of Fig. 9, the electron density of HOMO, HOMO-1, LUMO and LUMO+1 is mostly located at double bonds ($-C=C-$) of carbon nanotube and the main electronic transition of this complex corresponds to $\pi \rightarrow \pi^*$ transitions.

Comparing the $\lambda_{\max}$ of Remdesivir and complex “d” shows that adsorption of the drug on the CNT(5,5) changes the value of $\lambda_{\max}$ and after interaction of Remdesivir with the CNT(5,5), the $\lambda_{\max}$ is increased.

Moreover, as observed in Table 6 and Fig. 8, the $\lambda_{\max}$ of the COOH-functionalized CNT/Remdesivir, S-doped CNT/Remdesivir, Si-doped CNT/Remdesivir and Al-doped CNT/Remdesivir complexes, have been obtained at 596.46, 570.35, 606.63 and 600.04 nm, with the oscillator strength $f = 0.14, 0.16, 0.23$ and 0.15 , respectively. Also, the main transition of these complexes are associated to the $(H-1 \rightarrow L+1)$,

(H $\rightarrow$ L+4), (H-1 $\rightarrow$ L+1) and (H-1 $\rightarrow$ L+1), respectively. All the main electronic transition of these complexes are related to $\pi\rightarrow\pi^*$ transitions. On the basis of these results, it is concluded that doping CNT with the dopant atoms and functionalization with COOH group, increases the maximum absorption bands ($\lambda_{\max}$) of these complexes relative to the pristine CNT/Remdesivir complex. The obtained results show that the calculated maximum absorption bands ($\lambda_{\max}$) and oscillator strength of the Si-doped CNT/Remdesivir complex is higher than those of the other functionalized and doped CNTs complexes, which these adsorption properties are in agreement with the other properties which have been discussed in the previous sections.

4. Conclusions

In this work, DFT and TDDFT calculations were carried out to investigate the interactions between pristine CNT(5,5) and also COOH functionalized CNT and S-, Si- and Al-doped CNTs with Remdesivir to investigate the complexes as drug delivery systems. The highest negative value of adsorption energy among various configurations of this drug and simple CNT(5,5) has been reported for complex “d”, that displays that this structure is the most stable structure among the other configurations. Enhancement of electrophilicity index of the CNT/Remdesivir complex compared to the single Remdesivir and simple CNT(5,5) in the solvent phase, shows that the interaction of Remdesivir with CNT(5,5) created more electrophilic property for the studied structure. The adsorption of Remdesivir on CNT(5,5), enhances the values of dipole moments in the both phases that is a favorite property for drug delivery. Complex “d” as the most stable structure was investigated to consider the effects of S-, Si- and Al- doped CNT(5,5) and COOH functionalized CNT(5,5) on the adsorption behavior of Remdesivir. The more negative values of adsorption energies of adsorption of Remdesivir on the functionalized and doped CNTs compared to the pristine CNT, show that the weak interaction of pristine CNT and Remdesivir was altered to strong interaction through functionalization and doping the CNT. The most negative value of adsorption energy was reported for the Si-doped CNT/Remdesivir complex, that indicates that the interaction between the Si-doped CNT and Remdesivir is stronger relative to the other compounds. The solvation energies of these complexes show that the Si dopant atom increases the solubility because of the highest solvation energies. The smallest value of E_g of the Si-doped CNT/Remdesivir complex and therefore its smallest chemical hardness causes the higher reactivity of this complex compared to the other complexes.

Also, the conductivity of the Si-doped CNT/Remdesivir compound is greater than the other compounds because of higher decrease of E_g value which is consistent with higher reactivity of this structure. The values of μ , ω and ECT of the Si-doped CNT/Remdesivir compound is greater than the other structures, which can be associated to the highest positive charge of Si atom relative to the other dopant atoms.

Moreover, The more negative values of thermodynamic quantities such as Gibbs free energy changes (ΔG) and enthalpy changes (ΔH) for Remdesivir adsorption on the functionalized and doped CNTs compared to Remdesivir adsorption on the pristine CNT show that the adsorption of the drug on the functionalized and doped CNTs is more thermodynamically desirable. Among these complexes, the Si-doped CNT/Remdesivir complex shows the most negative ΔG and ΔH , similar to the results of the adsorption energies. Besides, the IR spectra obtained by frequency calculations show that the Si-doped CNT/Remdesivir complex has higher frequencies compared to the other complexes. Also, excited state calculations, show that the $\lambda_{\max}$ and oscillator strength of the Si-doped CNT/Remdesivir complex are larger than those of the other complexes that these adsorption properties are in good agreement with the other investigated properties.

According to all the obtained results it is concluded that the Si-doped CNT is the best nano vehicles for Remdesivir drug delivery compared to the pristine CNT and the other functionalized and doped CNTs investigated in this study, because of its better reactivity, better energetic,

electronic, adsorption and thermodynamic properties.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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