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How Do Palladium Complexes Affect on Coil Structure of Human Serum Albumin in the Presence of Carbon Nanotube? A Molecular Dynamics Study

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To investigate the interaction and adsorption of drug and carbon nanotube on human serum albumin, three anti-cancer drugs ([Pd(phen)(R-gly)]NO_3, R = methyl, propyl and amyl) with different hydrophobic tails and anticancer activities were selected. These drugs have better anti-tumor activity and less side effects than that known *cis*-platinum drug. Human serum albumin is also important for drug delivery and release and acts as carrier of internal biological molecules and external drugs that bind to many drugs in blood route and carry them. Drug binding to human serum albumin can change its helicity and this can affect on the drug release and distribution. Thus, study of this aspect can provide structural features determining the therapeutic efficiency of drug that has the least effect on human serum albumin helix structure. Interaction of three drugs with human serum albumin was investigated by molecular dynamics simulation and the best drug with the least denaturation effect was selected to compare its effect in the presence of nanotube. The structure of protein was again compared in the presence of drug and nanotube. The results revealed less denaturation effect of methyl on human serum albumin structure. The denaturation of protein also decreased more in the presence of nanotube. Carbon nanotube can be used as a cover for denaturation effect of drug and leads to better orientation and less random movement of drug around protein. It also reveals drug interaction with protein binding site facilitated in the presence of carbon nanotube.

Keywords: Molecular dynamics simulation, Human serum albumin (HSA), Helix, Carbon nanotube (CNT), Denaturation

INTRODUCTION

Due to application of nanotechnology and nanoscience in medicine, drug delivery, tumor therapy and production of improved biocompatible drugs [1], much of the current research work is aimed at the investigation of drugs which have fewer side effects and are active against a broad range of cancers. Carbon nanotubes (CNTs) have the potential application as drug carrier to get the drug at target place without side effect on non-diseased cells that is the major challenge in drug delivery systems. They have unique structural properties making them promising for biomedical applications [2].

The other important challenge in drug delivery is biocompatibility or biosafety of delivered drugs and drug carriers to human body [3,4]. Poland *et al.* [5] have shown formation of granulomas or pathogenic behaviors like inflammation of tissues exposing to CNT. Bay *et al.* [6] have shown testis damage to tail of mouse in treating the vein by CNTs. Thus, designing biosafety systems for drug delivery is of urgent importance.

On the other hand, interaction of drug carriers and macromolecules like proteins has also attracted attention in recent years due to biocompatibility challenge. It can throw light on cytotoxicity and biosafety of drugs and CNTs. Abundant plasma protein of human serum albumin (HSA)

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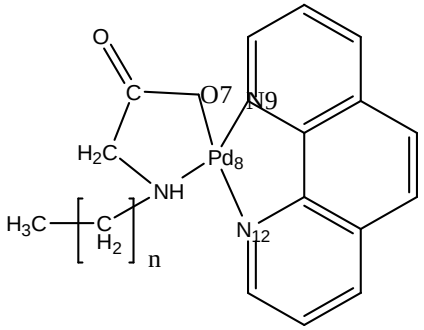
can transport various molecules and drugs such as fatty acids, hormones and toxic metabolites. It can also deliver drugs to targeted cells by binding them to HSA and can be used as drug carrier to specific receptors in targeted drug delivery by targeting and decreasing the side effects of drugs [7,8]. Amino acids in 507-749 regions are located in active site of HSA [9]. Rollet *et al*. [10] have shown sonochemical preparation of HSA nanocapsules without toxic cross linking chemicals and emulsifiers. They have used it as targeted folic acid delivery to chronically activated macrophages. Balavoine *et al.* [11] showed experimentally that protein streptavidin maintain its native helix structure on CNT surface. The important of hydrophobic residues distribution on CNT determines the chymotrypsin and soybean peroxidase conformational changes during their adsorption on CNT as argued by Karajanagi *et al*. [12] using atomic force microscope and Fourier transforms infrared spectroscopies.

In addition, the CNT effect on conformation and function of proline rich motifs has been investigated by molecular dynamics simulation. It has been found that nanotube can plug into the hydrophobic core of protein and damage the original function of protein *via* π-π interaction [13]. However, the mechanism, particularly the effect of CNTs on the structure and function of biomolecules which may lead to coating of proteins, is far from being understood.

Yet, with all progress, even the advanced medications have undesired side effects due to interaction of drug with non-targeted proteins and biomolecules and this challenge limit our potential to treat diseases such as cancer and infectious diseases. New synthesized complexes of [Pd(phen)(R-gly)]NO_3, where R-gly is methyl-, propyl-, and amyl-glycine have improved anticancer effect and less side effect than that of cisplatin antitumor complexes to treat gastrointestinal tract diseases. The structure of [Pd(phen)(R-gly)]NO_3 is presented in Fig. 1. But these metal complexes have some cytotoxicity or side effects on body [14]. Moreover, the HSA, as carrier of these drugs in gastrointestinal tract, is usually denatured due to drug interaction with these drugs; leading to unknown problems. Gastrointestinal tract is more vulnerable to foreign molecules and drugs. The proteins in targeted drug delivery can be covered by a protective coat and the coating may



n=0, 2, 4

Fig. 1. Structure of methyl, propyl and amyl glycine Complexes.

reduce protein conformational changes caused by probable interaction between these agents and facilitate the targeted drug delivery with fewer side effects. Thus studies on binding of such coating agents with proteins are important.

This paper studies the interaction of three above mentioned palladium complexes and HSA as drug carrier and their effects on protein structure and function using molecular dynamics simulation. Molecular dynamics (MD) simulation as an effective method of studying bio molecules [15] and nano systems [16] has been used to provide an insight from interaction. The interaction of proteins and drugs on active site is important in the function of protein. Thus, this interaction is investigated in the presence of CNT as a coating agent for drug undesired effects.

MATERIAL AND METHODS

Molecular Dynamics Simulation

To obtain optimal geometry for electrostatic potential calculations, [Pd(phen)(R-gly)]NO_3 structures were first optimized with the help of HyperChem 7 software [17] using semi-empirical AM1 method [18]. For GROMOS96 53a6 force field, charges and atom types of [Pd(phen)(R-gly)]NO_3 were fully parameterized by Dundee PRODRG2.5 Server [19]. TubeGen 3.4 [20] online server was used to generate geometrical coordinate parameters of uncapped armchair carbon nanotubes (CNT) with chirality of (10, 7) (with a 1.4 diameter and 1.9 nm lengths).

Five Pd(phen)(methylgly)]NO_3 and one CNT and a HSA were placed in a 760 nm^3 box of around 4000 water molecules with 3 nm distance between the solute and box. Periodic boundary condition was imposed in three directions [21]. 0.9 nm cut-off for both vdW and electrostatic interactions were used. Long range electrostatic interaction was computed by the particle-mesh Ewald summation method [22]. Equation of motion was integrated using a leap-frog algorithm with a time step 1 fs. The non-bonded interaction pair list was updated every 10 fs with the cut-off of 0.9 nm. All systems were neutralized by adding counter-ions and then minimized to remove bad vdW contacts with water. The simulation box was solvated with SPC/E water model. Constant temperature of 300 K was enforced using nose-hoover algorithm [23] with a damping coefficient of 0.1 ps. Parrinello-Rahman pressure coupling[24] was used in NPT run for 1 atm with the damping coefficient of 0.1 ps. Final NPT simulations of 40 ns were carried out using GROMACS suit with Gromacs-4.5.4 package [25]. LINCS algorithm was used to constrain all bonds, including hydrogen bonds [26]. Grid algorithm was used to search neighbors. Position restraint was used to allow relaxation of water molecules for 1 ns [27]. HSA structure was taken from protein data bank with 1AO6 pdb id code [28]. VADAR was used to get helix and coil structure [29]. Table 1 lists a summary of the simulations.

Insertion of Palladium Parameters

Constants for Ryckaert-Bellemans potential (C_0-C_5) were needed for palladium simulation. Metal parameters were calculated manually and inserted in related topology files of molecular dynamics simulation. The structures were optimized with gauss view. The Lennard-Jones parameters for the palladium were calculated from Gaussian software obtained with density functional theory (DFT) B3LYP method and 6-311++G(d,p) basis set [30]. Palladium relative charge was 0.5698 and its mass was about 106.4 and inserted manually. The following equations were used to calculate C_0, C_1, … .

$$C_0 = F_2 + \frac{1}{2(F_1 + F_3)} \quad (7)$$

$$C_1 = \frac{1}{2(-F_1 + 3F_3)} \quad (8)$$

Table 1. Summary of Set up Systems (Duration of all Systems was 3 × 40 ns)

No.	System	No. water	No. Complex
1	HSA+ Pd(phen)(methylgly)]NO_3	4167	5
2	HSA+ Pd(phen)(methylgly)]NO_3	4155	5
3	HSA+ Pd(phen)(methylgly)]NO_3	4143	5
4	HSA+CNT (10, 7)	4015	0
5	HSA+CNT (10, 7)+ Pd(phen)(methylgly)]NO_3	3746	5
6	HSA	4254	0

$$C_2 = -F_2 + 4F_4 \quad (9)$$

$$C_3 = -2F_3 \quad (10)$$

$$C_4 = -4F_4 \quad (11)$$

$$C_5 = 0 \quad (12)$$

F_i is the force on particle i (F_1 is the force between atoms 8 and 12, F_2 is between atoms 8 and 7, F_3 is between 8 and 9 and F_4 is between 8 and 3, which atom number 8 is palladium and number 3 is nitrogen, number 7 is oxygen, number 9 and 12 are nitrogen connected to palladium (shown in Fig. 1)). Bond stretching between atoms i and j with harmonic potential were obtained from following equations:

$$V_b(r_{ij}) = \frac{1}{2}k_{ij}^b(r_{ij} - b_{ij})^2 \quad (13)$$

with the force given by:

$$F_i(r_{ij}) = k_{ij}^b \frac{(r_{ij} - b_{ij})r_{ij}}{r_{ij}} \quad (14)$$

where k_{ij} is the harmonic force constant, b_{ij} is the equilibrium distance in nm and r_{ij} is the distance between i and the nearest image of j.

Bond lengths and force constants were obtained from the optimized structure in Gaussian software, and Table 2 presents the results.

RESULTS AND DISCUSSION

Interaction of Human Serum Albumin and Three Methyl, Propyl and Amyl Glycine Complexes

Interaction of HSA with three drugs was first conducted. Figure 2 shows a snapshot of interaction in the presence of methyl complex.

Drug is in a far good distance from HSA at the beginning of simulation and during the simulation time from 3-10 ns, drug molecule fluctuates around protein and shows little interaction with amino acids. Drug undergoes structural changes in order to achieve HSA during 10 ns. At 20 ns, drug shows tendency to bind to amino acids. At 40 ns, drug locates on HSA and complete interaction occurs. Other drugs also show the same result and are not shown here.

RMSD of system (HSA, drug complex and solvent) is

Table 2. Bond Length and Force Constant of Palladium and Nitrogen Obtained from Gaussian Program

Atoms	Force constant (m Dyn A^{-1})	Bond length (A)
Pd- N[a]	1.92	1.93
Pd-O	1.94	1.88
Pd-N[a]	2.17	1.93
Pd-N[b]	1.19	1.96

[a]Bond length and force constant of Pd-N of cyclohexane ring
[b]Bond length and c of Pd-N of cyclopentane ring.

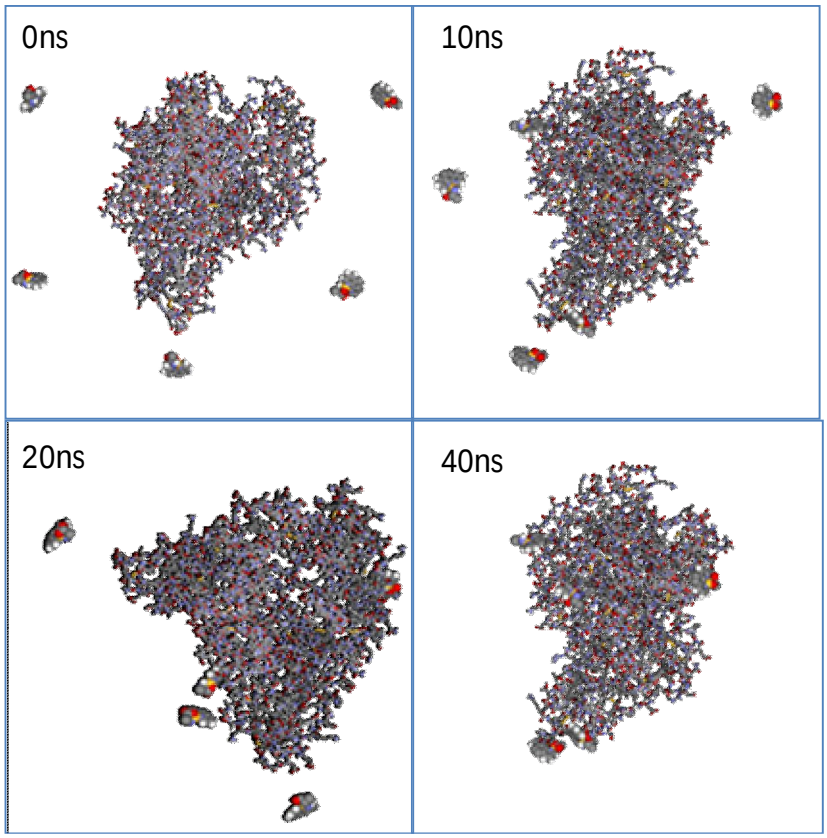


Fig. 2. Snapshot picture taken by DS Visualizer from HSA interaction with methyl complex.

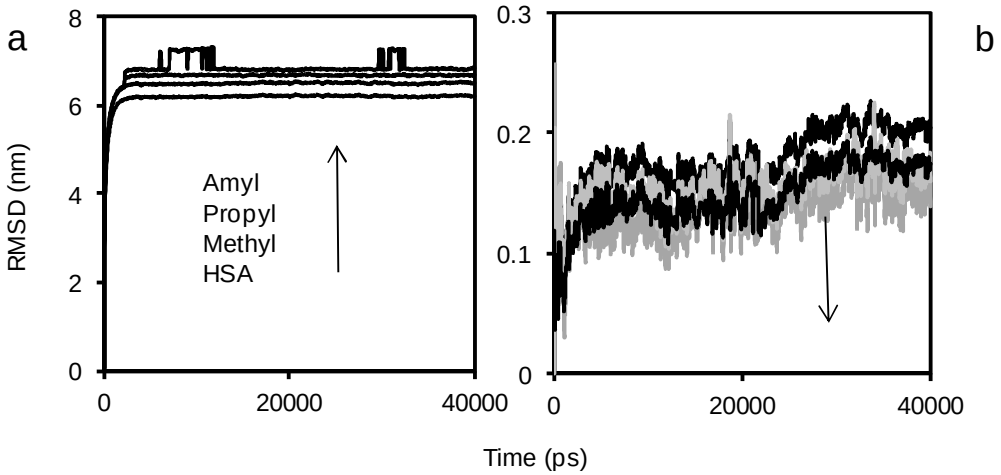


Fig. 3. RMSD of a) system and b) protein.

displayed in the presence and absence of drug (Fig. 3). Average value of RMSD for protein is 0.15 nm. RMSD curve shows fluctuation during 5 ns and after close interaction of drug with HSA, RMSD is flatted. Figure 3a shows more structure deviation of system in the presence of amyl complex. It reveals that by the increase of hydrophobicity of drug, the structure deviation of system increases. Less average of RMSD is confirmed in the absence of drug. Figure 3b shows the same trend for RMSD of protein. It confirms that more structure deviation of protein is associated with the increase of hydrophobicity of the complex.

The results of hydrogen bonds between protein and solvent in the presence and absence of three complexes (Fig. 4a) reveal the decrease of hydrogen bond by increasing hydrophobicity of the complex. This could be due to stronger interaction between water and HSA and formation of hydrated layer that exclude drug from protein surface. Hydrogen bond is further reduced in the presence of amyl complex due to more interaction of amyl with HSA.

RDF of solvent around HSA (Fig. 4b) in the presence of all complexes shows formation of hydrated layer around protein while excluding the drug molecules from protein surface and this effect is maximum for amyl complex. It can be in agreement with more hydrogen bonds with water. Figure 4c shows RDF of drugs around each other which

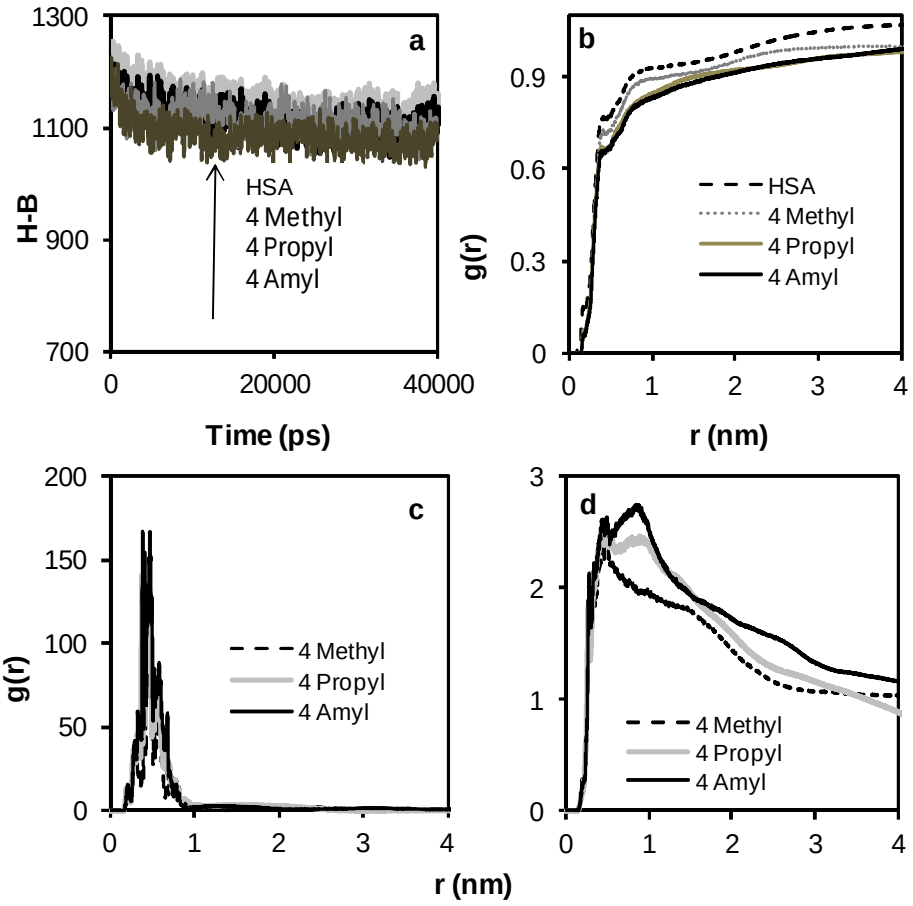


Fig. 4. a) Hydrogen bond variations between protein and water in the presence and absence of complexes. RDF curve of b) solvent around protein, c) drug around drug, d) drug around protein.

reveals more self aggregation tendency of more hydrophobe or long tail complexes. RDF of drug around HSA (Fig. 4d) shows more tendency of amyl complex to change structure of protein. Thus, methyl complex has less effect on HSA structure and is a better drug with less side effects. RDF of drug around protein (Fig. 4d) clarifies their interaction. It confirms above results.

It can be concluded that a hydrated layer is formed on protein surface. By approaching the drug to this layer, the number of water molecules near protein is reduced and drug approach protein and induce structure changes. The structure changes of protein are more in the presence of amyl complex.

Solvent accessible surface area of protein during 40 ns is depicted in Fig. 5a. More area of protein or less intermolecular hydrogen bond of protein in the presence of amyl complex confirms more denaturation or structural changes of protein by this hydrophobe complex. Totally, amyl has more structural changes and denatures protein more than methyl. Topology files of molecular dynamic simulation were inserted in VADAR site and beta, coil and helix percentage obtained in the presence and absence of three complexes. Results are displayed in Figs. 5b-d.

Results show reduction of helix and increase of coil in the presence of all complexes and beta structure does not show any significant changes. More helix reduction and coil increase in the presence of amyl complex reveal its more effect on protein structure. According to above results, methyl complex has the least effect on helix structure of HSA and has less denaturation effect. The nature of interaction between protein and drugs is due to hydrophobe interactions that are more in amyl complex. The reduction

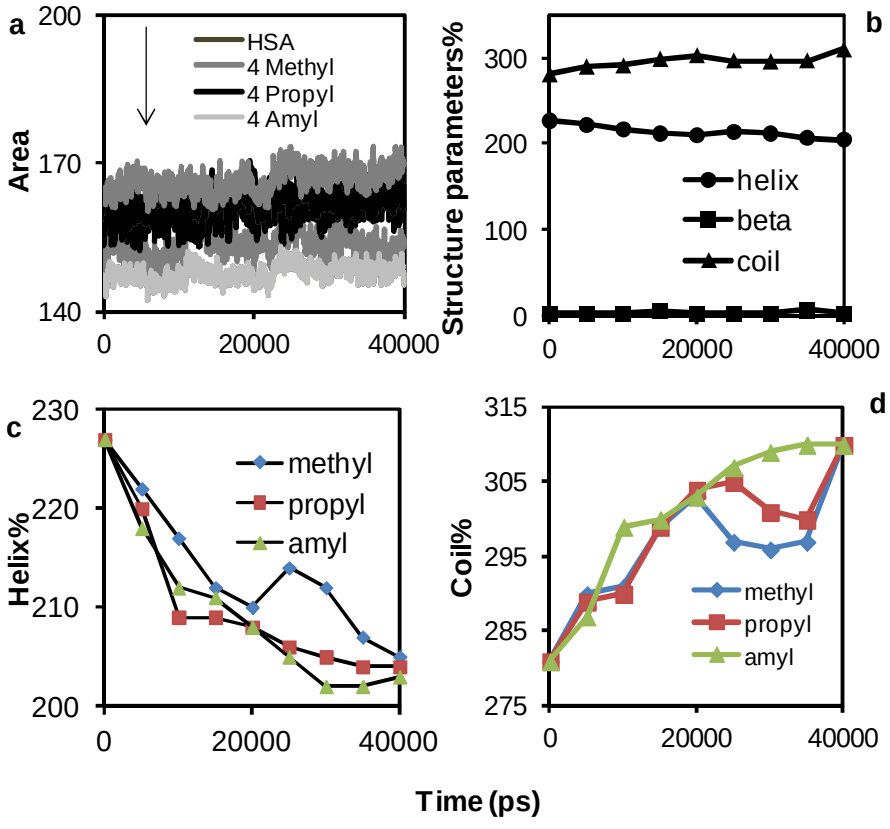


Fig. 5. a) Solvent accessible surface area of protein in the presence and absence of drug b) structural changes, c) helix changes, d) coil changes of protein in the presence of methyl complex.

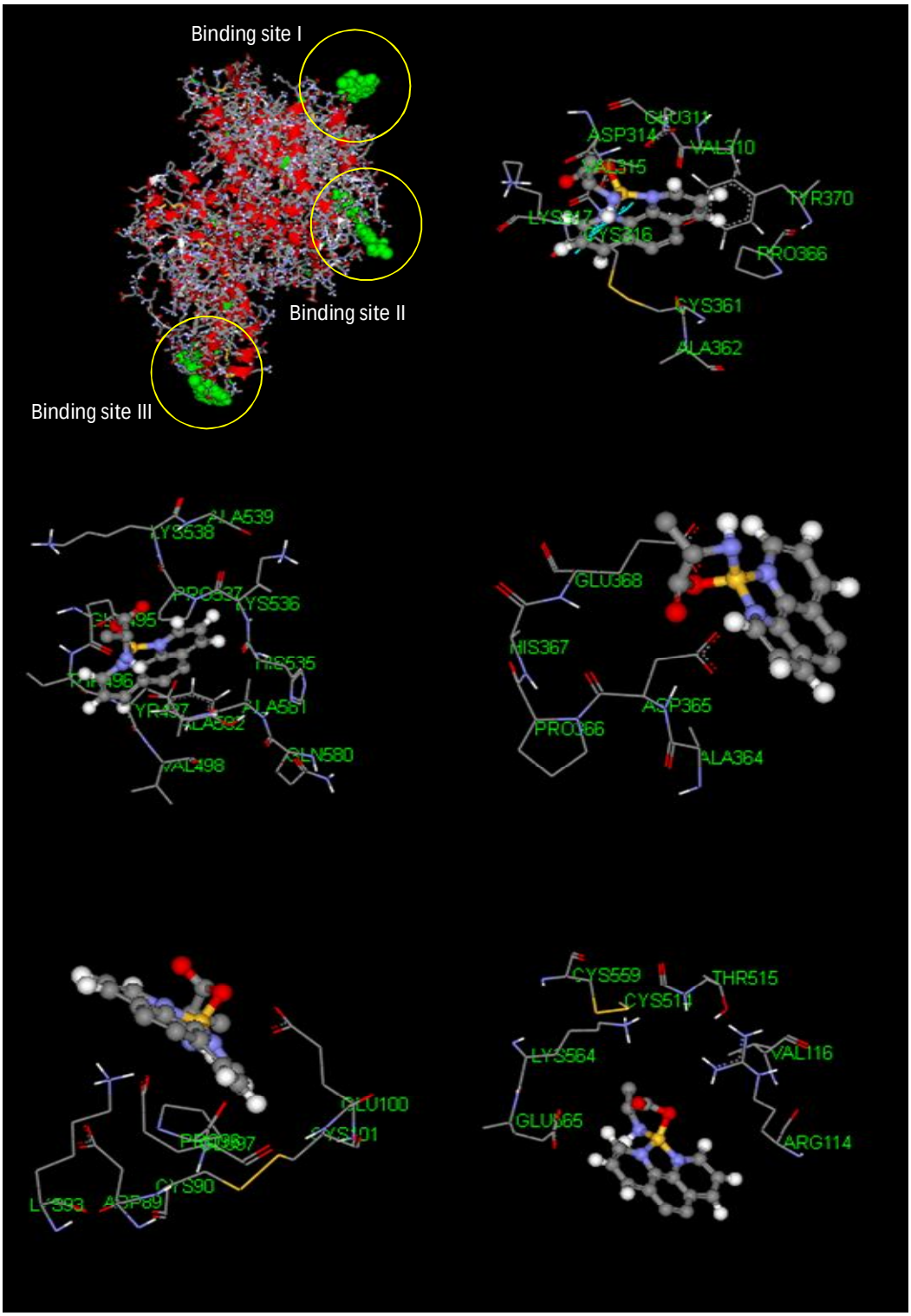


Fig. 6. a-e) Three binding sites, I, II and III, of methyl complexes to protein (yellow circles) and extension of amino acids corresponding to the binding sites of five methyl complexes.

of helix structure is observed in the presence of methyl complex and more reduction of helix structure is observed in the presence of CNT. In the next section, the interaction of protein with CNT is studied.

The interaction between HSA residue and methyl complex is exhibited in Fig. 6. Table 3 clearly presents the interacted residues of protein with five ethyl, propyl and amyl complexes represented with ligand 1-5. Results reveal that smaller drug with less hydrophobic property (methyl complex) can penetrate to the active site and bound to

Table 3. Interacted Amino Acids with Five Methyl, Propyl and Amyl Complexes

	Methyl
Ligand 1	VAL310, GLU311, ASP314, VAL315, CYS316, LYS317, CYS361, ALA362, TYR370, PRO366
Ligand 2	LYS536, PRO537, LYS538, ALA539, GLU580, ALA581, ALA582, GLU595
Ligand 3	ALA364, ASP365, PRO366, HIS367, GLU368
Ligand 4	ASP89, LYS90, LYS93, PRO97, GLU98, GLU100, CYS101
Ligand 5	ARG114, VAL116, CYS514, THR515, CYS559, LYS564, GLU565
	Propyl
Ligand 1	ALA364, ASP365, GLU368, LYS372
Ligand 2	ASN44, GLU45, VAL46, THR47, GLU48, ALA50, LYS51
Ligand 3	ALA55, ASP56, GLU57, SER58, ALA59
Ligand 4	GLU6, GLU60, CYS62, ASP63, LYS64, SER65
Ligand 5	LYS557, CYS558, LYS560, ALA561, ASP562, ASP563, LYS564
	Amyl
Ligand 1	PHE502, ASN503, ALA504, THR508, LYS573, LYS574, ALA577
Ligand 2	ARG114, LEU115, VAL116, ARG117, LYS137
Ligand 3	ASP121, VAL122, THR125, LYS174
Ligand 4	GLU501, PHE502, ASN503, VAL576, ALA577, ALA578, SER579
Ligand 5	LYS541, GLU542, GLN543, LEU544, LYS545, ALA546

amino acids located near this site.

CNT Interaction with HSA

SWCNT (10, 7) was used as a model system to understand the interaction of CNT with HSA. The diameter of CNT is selected in such a way that to be enough to investigate its interaction with protein. Snapshot picture is taken from the system and presented in Fig. 7.

Fluctuation of CNT around protein is observed during simulation time. No significant structural change of protein is observed in CNT and protein. RMSD of protein, CNT and system is calculated to investigate the interaction of CNT with protein (Fig. 8a). No significant change is observed for RMSD of CNT and protein and its value is about 0.4 nm. RMSD of systems show some fluctuation that can be due to water molecules interacting with other parts of system.

Distance of CNT and protein (Fig. 8b) shows CNT tendency to interact with HSA at 0.6 nm. The reduction of distance shows the increase of interaction. The nanotube fluctuation near the active site after 40 ns and the noncovalent interaction between nanotube and residues namely ARG114, VAL116, ARG117, PRO118, GLU119, ALA511, ASP512, CYS514, THR515, CYS558, CYS559, LYS560, ALA561, ASP562, ASP563, LYS564, GLU565 are possible. Results show that drug is located near the active site. Although drug does not enter into the active site of protein, it can bind to protein in a more effective way in

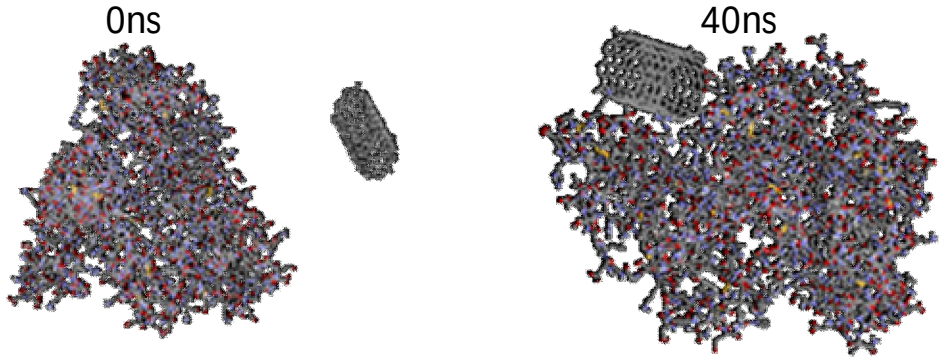


Fig. 7. Snapshot picture of CNT interacting with HSA.

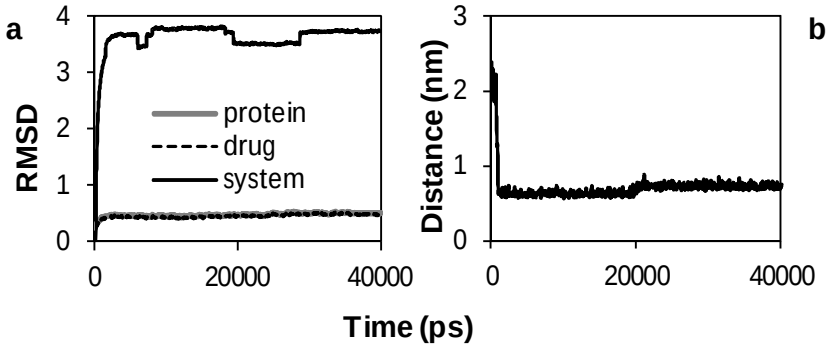


Fig. 8. a) RMSD of CNT, protein and system, b) distance between mass centers of CNT and HSA.

the presence of nanotube (near active site).

Interaction of Methyl Complexes with HSA in the Presence of CNT

Snapshot picture of system during 40 ns is depicted in Fig. 9. During 10 ns, drug approached CNT, though no significant interaction was observed. Around 12 ns, drug inclined to stay far from the aggregated conformation and to interact with protein. Fluctuation in drug position helps drug to get close to CNT side wall, so that after 40 ns, drug and CNT stayed on protein surface. CNT helps stable drug movement around protein by limitation of its free movement and also helps drug stays near binding site of protein instead of random fluctuation on protein surface.

RMSD of protein (Fig. 10a) confirms flat curve without structure changes in the presence of nanotube. In the system including CNT/drug/HSA, RMSD does not change over 0-100 ps, then it increases and after 6 ns becomes flat indicating lack of structural changes of protein. Distance between mass centers of protein and CNT or drug (Fig. 10b) shows the decrease of distance or getting close the drug and CNT to protein. In order to investigate effect of drug on protein structure in the presence of CNT, helix and coil changes were obtained (Figs. 10c, d). Results show reduction of helix structure in all cases but less reduction of helix is observed in the presence of CNT. In the presence of CNT, protein structure is denatured less and helix percentage is more with less coil change. When the drug is added to protein system in the presence of CNT, CNT reduces denaturation effect of drug and the helix percentage is more compared to that of the absence of CNT. The coil values also confirm more denaturation effect of methyl complex in the absence of CNT. CNT makes drug close to protein and also somewhat coats its negative denaturation effect.

Therefore, CNT helps less random movement of drug

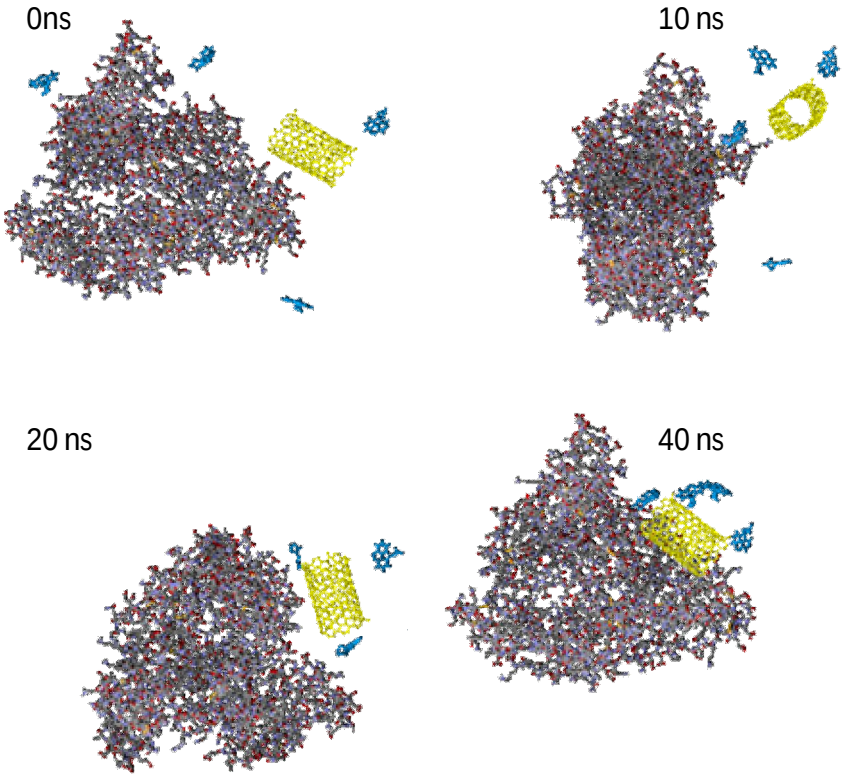


Fig. 9. Snapshot of protein/drug/CNT interaction during 40 ns.

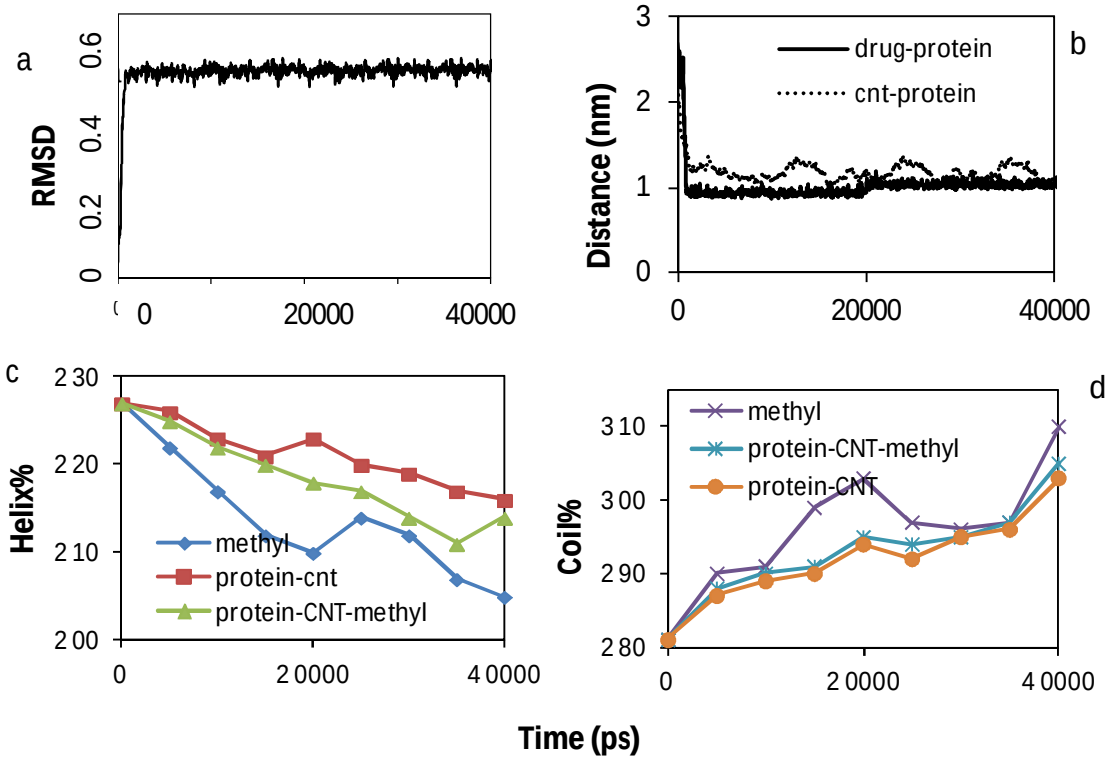


Fig. 10. a) RMSD of protein, b) distance between mass centers of drug/CNT and protein. c) Helix and d) coil percentage of protein in the presence of drug and CNT.

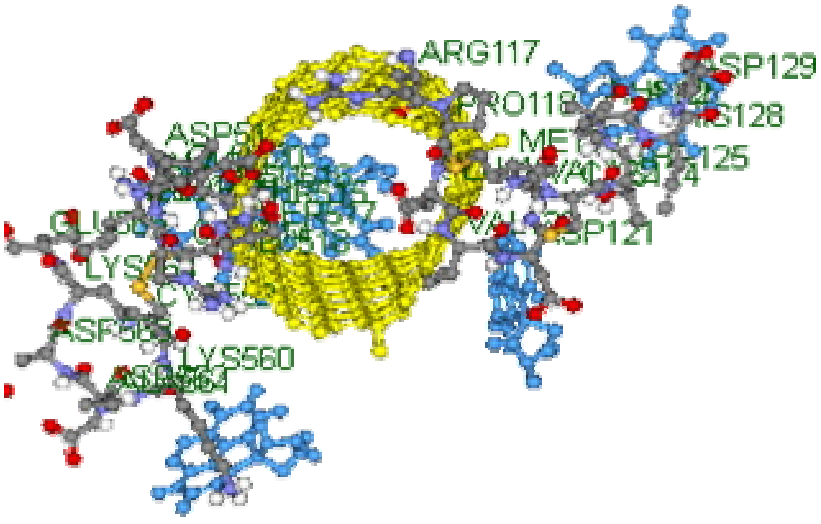


Fig. 11. The interaction between CNT, methyl complex and residues of HSA.

and good orientation of drug to adsorb on protein surface. Drug/CNT is located near binding site of protein during simulation and interact with its amino acids. So CNT can be used as suitable carrier in drug delivery and targeted drug release under drug control and causes drug interaction with protein with less denaturation effect. Methyl complex has the less denaturation effects among other drugs and its denaturation effect decreased in the presence of CNT. Due to less reduction of helix structure while reducing the distance between drug and protein in the presence of CNT compared to the system in the absence of CNT, drug-CNT can be used as a suitable carrier in drug delivery. Human serum album is a protein carrier with specific receptors that selectively bind to a special cell. So, it can help targeted drug delivery and release. The reduction of helix structure of protein in the presence of CNT reveals drug interaction with protein with less denaturation effect in the presence of CNT.

The residues in close contact with methyl complex and CNT during the 40 ns simulation are observed in Fig. 11. It illustrates the interaction between residues of protein namely ARG117-ASP129, ALA511-ARG521, CYS559-GLU562 that are near the active site.

CONCLUSIONS

MD simulation was used to study the interaction between three palladium complexes with different hydrophobic tails on HSA structure. We also tried to select a complex with less effect on protein helix structure and compare its effect in the presence of CNT. Results revealed less denaturation effect of methyl complex on HSA structure due to its less hydrophobic tail and smaller size. Comparison of methyl effect on helix structure of protein in the presence of CNT demonstrated the reduction of denaturation due to CNT effect on less random movement of drug around protein and orienting the drug near the active site of protein. On the basis of our results, HSA can be used to control the location where the drug is released in the body and nanotube can be used to control the side effects and biocompatibility of drug on HSA as well as targeted delivery of drug to target.

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