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Assessment of Drug Delivery Systems from Molecular Dynamic Perspective

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Abstract**—**In this study, we developed and simulated nano-drug delivery systems efficacy in compare to free drug prescription. Computational models can be utilized to accelerate experimental steps and control the experiments high cost. Molecular dynamics simulation (MDS), in particular NAMD was utilized to better understand the anti-cancer drug interaction with cell membrane model. Paclitaxel (PTX) and dipalmitoylphosphatidylcholine (DPPC) were selected for the drug molecule and as a natural phospholipid nanocarrier, respectively. This work focused on two important interaction parameters between molecules in terms of center of mass (COM) and van der Waals interaction energy. Furthermore, we compared the simulation results of the PTX interaction with the cell membrane and the interaction of DPPC as a nanocarrier loaded by the drug with the cell membrane. The molecular dynamic analysis resulted in low energy between the nanocarrier and the cell membrane as well as significant decrease of COM amount in the nanocarrier and the cell membrane system during the interaction. Thus, the drug vehicle showed notably better interaction with the cell membrane in compared to free drug interaction with the cell membrane.

Keywords**—**Anti-cancer drug, center of Mass, interaction energy, molecular dynamics simulation, nanocarrier.

I. Introduction

DRUG delivery systems open new and novel horizons towards developing more effective and targeted treatments. In this field, the application of computational analysis to medicine and nanomedicine has the potential to significantly overcome many of the current limitations in diagnosis, treatment and management of several cancers [1]-[3]. This research area provides an opportunity to assess and distinguish information about an atomistic scale of molecules interactions using molecular simulations.

Cell membranes are often main and final barriers in drug delivery. However, it is not clear how most hydrophobic drugs (such as paclitaxel) and vehicles act in the vicinity of cell membranes [4]. Paclitaxel is the first identified microtubule-stabilizing agent and it is clinically used to treat several cancers [5]. It binds to the microtubule to promote polymerization of tubulin and shifts the assembly equilibrium, inducing mitotic arrest and consequent apoptosis [6]-[8]. This hydrophobic cancer drug aggregates in both hydrophobic and hydrophilic environments [9], [10]. Additionally, the poor water solubility of paclitaxel limits its clinical application, as other hydrophobic drugs. Therefore, significant efforts have been done in the nanocarrier formulations for hydrophobic drugs delivery [11]-[16]. Computational analysis of hydrophobic drugs individually and with nanocarrier transportation, which may affect the bioavailability, distribution and elimination of pharmaceutical active compounds, through the cell membrane, will help us to understand the fundamental interactions between the hydrophobic drug with cell membrane and also the nanocarrier with cell membrane, leading to the design of optimized drug delivery systems [17], [18].

Since the world is expected to face with about 20 million cases of various cancers in the next two decades [19], it is essential to study the specific interaction of anticancer drugs encapsulated within nanocarriers or prescribed individually with the cell membrane experimentally and computationally [20]. In this scope, the computational methods can help in visualizing and understanding some physical and bimolecular properties that derives the compatibility between the drug, the nanocarrier and the cell membrane.

In previous researches, the interaction of drugs with cell membranes and also their transportation through the cell membranes had been investigated [21]-[23]. Few studies focus on the molecular dynamics interaction of the drug encapsulated within the phospholipid nanocarrier with the cell membrane; however, a number of experimental strategies have been carried out to clarify the interaction of different types of drugs with several nanocarriers such as liposomes and dendrimers or investigate drug behavior close and through the cell membrane from the COM and interaction energy point of view. Jambeck et al. [23], Kang et al. [24], Cheng et al. [25], Salas et al. [22] and also Dai et al. [26] are some remarkable researchers studied drug delivery systems and pharmaceutics by molecular dynamics. In addition to this, it has been believed that using nanocarriers provided higher efficacy of anti-cancer drug through better interaction with membrane and facilitating hydrophobic anti-cancer drugs penetration in to the cancer cell which resulted in higher tumor shrinkage and death [27]-[29].

From experimental intermolecular interaction perspective, anti-cancer-loaded nanocarriers like liposomes have higher efficacy in treatment of some solid tumors in comparison with free drug, since solid tumors' passive targeting has been

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influenced through higher permeability and enhanced retention [27], [30]-[32], therefore, drug payloads delivered to tumors increase. The enhanced permeability and retention effect are because of defective vascular endothelial linings of growing tumors consequently gaps in the endothelium [33]. Moreover, the liposomes' time of residence in the tumor interstitial space becomes extended because of incomplete drainage of lymph in growing tumors. Resided liposomes in the interstitial space of tumor play their role through gradual antitumor drug releasing to provide antitumor activities [29]; however, simulation parameters were simplified which is one of the main disadvantages of simulation. In this regard, we only assessed molecular dynamic interactions including van der Waals energy and COM, in the surface of the cell membrane.

In this study, we analyzed the effect of nanocarrier in drug delivery systems computationally by MDS which can accelerate several experiments done in laboratories and manage their high cost. Furthermore, the common approaches were investigated; molecular dynamically free drug interaction with cell membrane was compared with the interaction of encapsulated drug with cell membrane as a drug delivery system. We characterized the molecular level interactions from the COM and van der Waals interaction energy perspectives of an anticancer drug paclitaxel and a DPPC as a phospholipid nanocarrier with a cell membrane model. Variant theoretical and computational approaches have been conducted to assess molecular-scale phenomena in drug delivery systems but the study covers the interactions of the nanocarrier and the individual paclitaxel with the cell membrane. In particular, the substantial insight of the present work was to show how MDS would be a better method to determine the adequate properties of nanocarrier in comparison with free drug prescription and also the compatibility of the paclitaxel with the phospholipid nanocarrier. In general, main objective of this paper is to present the efficacy of drug delivery systems using carriers for drugs transportation to the targeted point. Although, this was reported in the previous researches to some extent [21]-[25], this study is more comprehensive by considering three systems and comparing them with each other.

II. Materials and Methods

We used monolayer DPPC model for paclitaxel delivery (drug carrier) which is consisting of 3433 water and 59 DPPC molecules since it provides liposome like features in addition to accessibility primitive simulation data. Further, a single paclitaxel molecule and a bilayer cell membrane model were considered for the simulation as an anti-cancer drug and cell membrane, respectively. Three systems were analyzed: (a) The single paclitaxel molecule and monolayer DPPC as nanocarrier contained 1 paclitaxel molecule, 59 DPPC molecules and 3433 water molecules, (b) The encapsulated drug within nanocarrier (DPPC and paclitaxel merged and considered as an independent structure) interaction with a bilayer cell membrane model and (c) The interaction of free paclitaxel molecule with the cell membrane model. All interactions were analyzed on the surface of the cell membrane. All primary structures, the paclitaxel structure, the DPPC nanocarrier and the cell membrane have been obtained from protein data bank (PDB). The initial structures are modified using VMD1.9.1 package [34] based on classical CHARMM36 force field [35], [36], which is widely used in the biophysics studies. The CHARMM36 force field includes bending, stretching, angular and dihedral and electrostatic forces which is defined as (1). The water molecules have been removed in order not to be considered twice when the carrier is close to cell membrane after final solvation.

$$E=\sum_{bond}K_b(r-r_0)^2+\sum_{angles}K_\theta(\theta-\theta_0)^2+\sum_{dihedral}K_\phi[1+\cos(n\phi-\delta)]+\sum_{improper}K_\psi(\psi-\psi_0)^2 \\ +\sum_{i>j}4\varepsilon\left[\left(\frac{\sigma}{r}\right)^{12}-\left(\frac{\sigma}{r}\right)^{6}\right]+\sum_{i>j}\frac{q_iq_j}{4\varepsilon_0 r} \quad (1)$$

The first term of (1), energy function, shows stretches between bonding in which Kb is the bond force constant and $r-r_0$ is the distance between atoms that accounts for the atoms' movement from equilibrium. The second term is used to represent bond angles in which Kθ is the angle force constant and $\theta-\theta_0$ is the angle difference from equilibrium between 3 bonded atoms. The third term accounts for the dihedral; Kφ is the dihedral force constant, n is the function multiplicity, φ is the angle of dihedral and δ is the phase shift. The fourth term represents improper situation of atoms out of plane, where Kφ is the force constant and $\psi-\psi_0$ is the angle difference in out of plane condition. In the last two terms, ε, σ, r and q show the potential well depth, the finite distance at which the inter-particle potential is zero, the distance between the atoms and the atoms partial charges, respectively [37], [38]. The random model had been built as a considered simulation box (Fig. 1). Both the orientation and the position of the drug and the nanocarrier were random. The random model was constructed by randomly inserting paclitaxel molecules into the DPPC and then removing any overlapping DPPC molecules. The motion of the drug and the nanocarrier were based on Newton's Law.

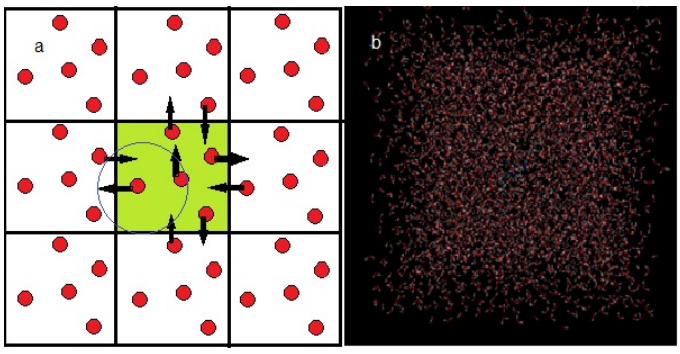

Fig. 1 (a) The schematic of simulation box (b) The simulation box including three systems within solvent (water molecules)

We considered the encapsulated paclitaxel within nanocarrier (merged drug and nanocarrier), and then the merged structure applied to the surface of the cell membrane.

To simplify, the interaction of the carrier with the cell membrane was investigated (Fig. 2 (a)). Furthermore, the interaction of the free anti-cancer drug paclitaxel and the cell membrane was investigated which was shown in Fig. 2 (b). To better understand the model, Figs. 2 (a) & (b) demonstrated the studding systems clearly.

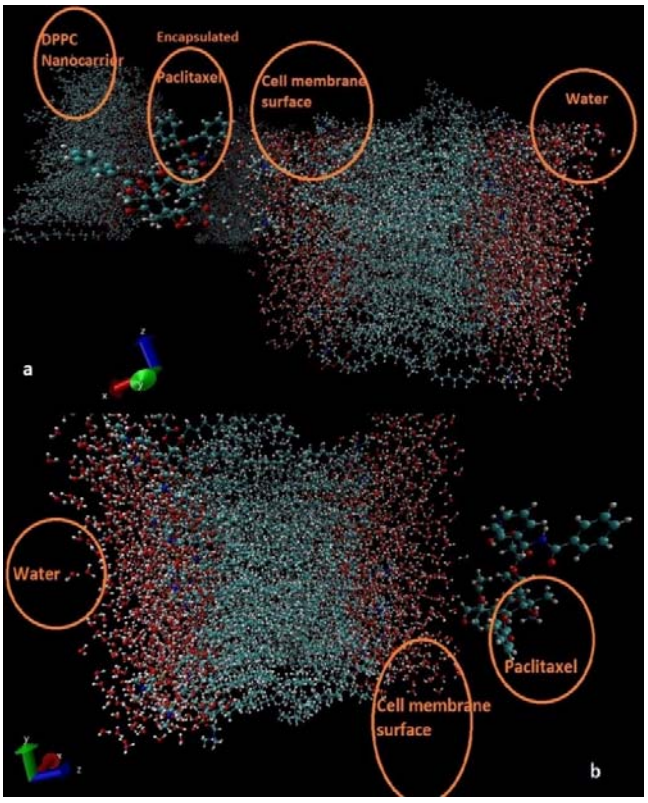

Fig. 2 (a) The interaction of the nanocarrier with the surface of the cell membrane (b) The interaction of the free paclitaxel with the cell membrane

All simulations were done in normal temperature and pressure (NPT) including average pressure 1.013 bar (coupled isotropically with a compressibility of 3 × 10^{-5} bar^{-1}) and temperature 310 K according to human body temperature [23] (2), (3):

$$T = \frac{2}{3Nk_B}\langle K \rangle \tag{2}$$

$$P = \frac{1}{V}\left[Nk_BT + \frac{1}{3}\left\langle \sum_{i>j} \vec{f}(r_{ij}).\vec{r}_{ij} \right\rangle \right] \tag{3}$$

where N is number of atoms, $\langle K \rangle$ is the average kinetic energy of the system and $\vec{f}(r_{ij})$ is the interaction force between i & j atoms in the system which are in r_{ij} distance, K_B is the Boltzmann constant, T the absolute temperature and V is system's volume. In accordance, the temperature and pressure depend on the atoms velocity and system's volume.

Langevin algorithm [39] has been used for temperature control and the Brandson algorithm [40] for pressure control. Van der Waals interactions and COM were modeled with a Lenard–Jones potential [41] by (4) in which ε is the potential well depth, σ represents the finite distance at the zero potential of inter-particle, r shows the distances between the atoms, and rm demonstrates the distance in a condition that the potential attains its minimum.

$$V_{LJ} = 4\varepsilon\left[\left(\frac{\sigma}{r}\right)^{12} - \left(\frac{\sigma}{r}\right)^{6}\right] = \varepsilon\left[\left(\frac{r_m}{r}\right)^{12} - 2\left(\frac{r_m}{r}\right)^{6}\right] \tag{4}$$

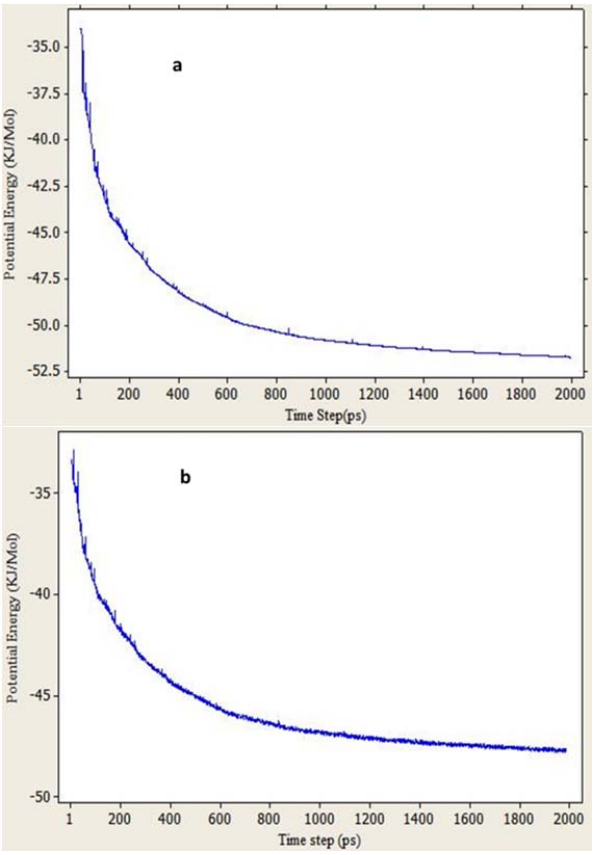

Fig. 3 (a) Minimization of primary energy level in the paclitaxel (b) Minimization of primary energy level in the nanocarrier

All molecules are not in aquatic environment naturally therefore they should be considered in human body condition which is aquatic environment. Based on this situation, obviously water should be considered in the systems. By considering aquatic environment, the primary energy changes, therefore, the energy must be minimized. In this study, the energy was minimized by the Conjugate gradients [42] method during 2000 ps to prepare the primary minimum energy level in the structure of the anti-cancer drug paclitaxel and the nanocarrier DPPC (Figs. 3 (a), (b)) as external components of systems, the primary energy level of the cell membrane had been considered minimum. Balance update was done in all three system components by increasing the primary 50 K temperature up to 310 K gradually in 5 steps until the group of control properties such as pressure and temperature become stable and permanent. The prime

temperature was assumed at 50 K in order to apply lowest molecular interactions and movements within each system and reset each of them.

The temperature and the pressure fluctuations of each system component were investigated in order to assure that all simulations carried out at 310 K. The temperature had few fluctuations around 310 K body temperature and approximately its average was equal to 310 K. The average temperature for the anti-cancer drug paclitaxel, the nanocarrier and the cell membrane was 309.39 K, 309.8 K and 309.15 K respectively. The average error in the temperature fluctuation was 1.3 which showed that all components of the system were in a proper temperature. In addition, according to the NPT ensemble, the pressure should be constant (1.013 bar) during simulation. The average pressure for the drug, the nanocarrier and the cell membrane was 1.022, 1.011 and 1.036 with that their average fluctuation error can be ignored.

The CHARMM36 force field [35], [36] was used for DPPC, [43]. For paclitaxel, the force field parameterized by Sept [44] was used. All simulations are performed using NAMD2.7 package [45]. NAMD uses the velocity Verlet method [45], [46] as default for NPT ensemble simulations. This method collects the position and velocity at the next time step from the current one by considering that the force is already computed. The velocity Verlet method is simple and time reversible, maintains linear and angular momentum, and needs only one force evaluation for each time step. The simulation box was considered with a full periodic boundary condition. Cubic simulation box with 26 cells in 3 dimensions has been considered as the periodic boundary condition. Each cell is 1 nm^3. The primary and major inputs included all parameters such as PDB file's information, force fields, and temperature and pressure algorithms. The drug and cell membrane, the nanocarrier and the cell membrane and also the drug and carrier systems were run for 400 ns. In order to extract the data presented in Figs. 4 and 5, the simulations were carried out 3 times (n=3) for each system.

The accuracy of the simulation as a default of the NAMD has been done by root-mean-square deviation (RMSD) or root-mean-square error (RMSE) using (5) at time t_2 with respect to a prime structure at time t_1:

$$RMSD(t_1, t_2) = \sqrt{\frac{1}{N}\sum_{i=1}^{N}\|x_i(t_2) - x_i(t_1)\|^2} \quad (5)$$

x_i (t) is the position of atom i at time t and N is the total number of atoms in the molecule. Often, the first frame of a trajectory (t_1) is used as a reference, and values of RMSD(t_1, t_2) are computed for all successive ($t_2 > t_1$) frames [47]. The deviation was computed as 0.91, 1.18 and 0.95 angstrom for interaction energy and 0.92, 1.23 and 0.92 angstrom for COM, in all assessed and simulated interactions including (a) the anti-cancer drug (paclitaxel) and the nanocarrier, (b) the drug and the cell membrane, and (c) the nanocarrier and the cell membrane, respectively. The maximum RMSD value shows the unstable interaction, fluctuations and jumps between molecules [48].

III. Results

MDS was utilized to acquire molecular dynamically data of van der Waals energy and normalized COM distance in the three abovementioned systems. In all systems, some fluctuations and downturn were observed that indicate the interaction between components of systems.

The computed van der Waals energy during the interaction, named interaction energy, was graphed for three systems of (a) paclitaxel and the cell membrane, (b) the paclitaxel and DPPC as a nanocarrier and also (c) the nanocarrier and the cell membrane in Figs. 4 (a), (b) and (c), respectively.

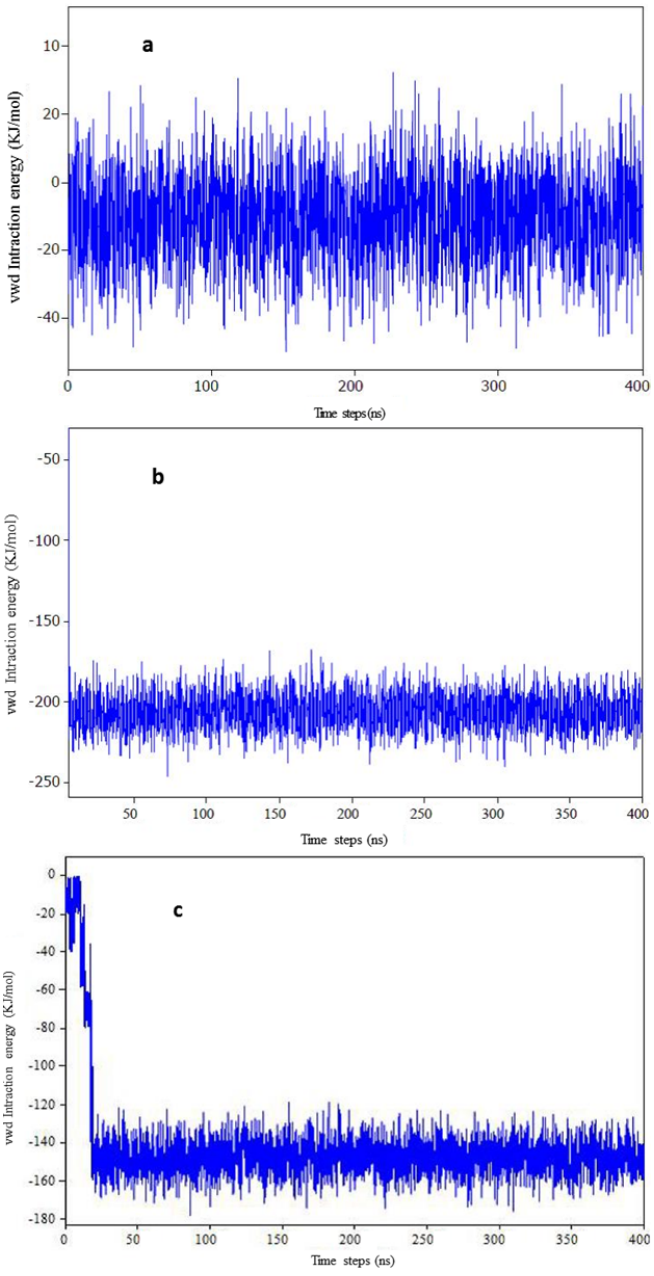

Fig. 4 (a) Anti-cancer drug paclitaxel and cell membrane interaction energy (b) The anti-cancer drug paclitaxel and the nanocarrier DPPC interaction energy (c) The nanocarrier DPPC and cell membrane interaction energy

In order to better investigate, the normalized COM distance was computed for all systems which are shown in Figs. 5 (a) (normalized COM distance between the drug and the cell membrane), (b) (COM distance between the nanocarrier and the cell membrane) and (c) (COM distance between the drug and the nanocarrier).

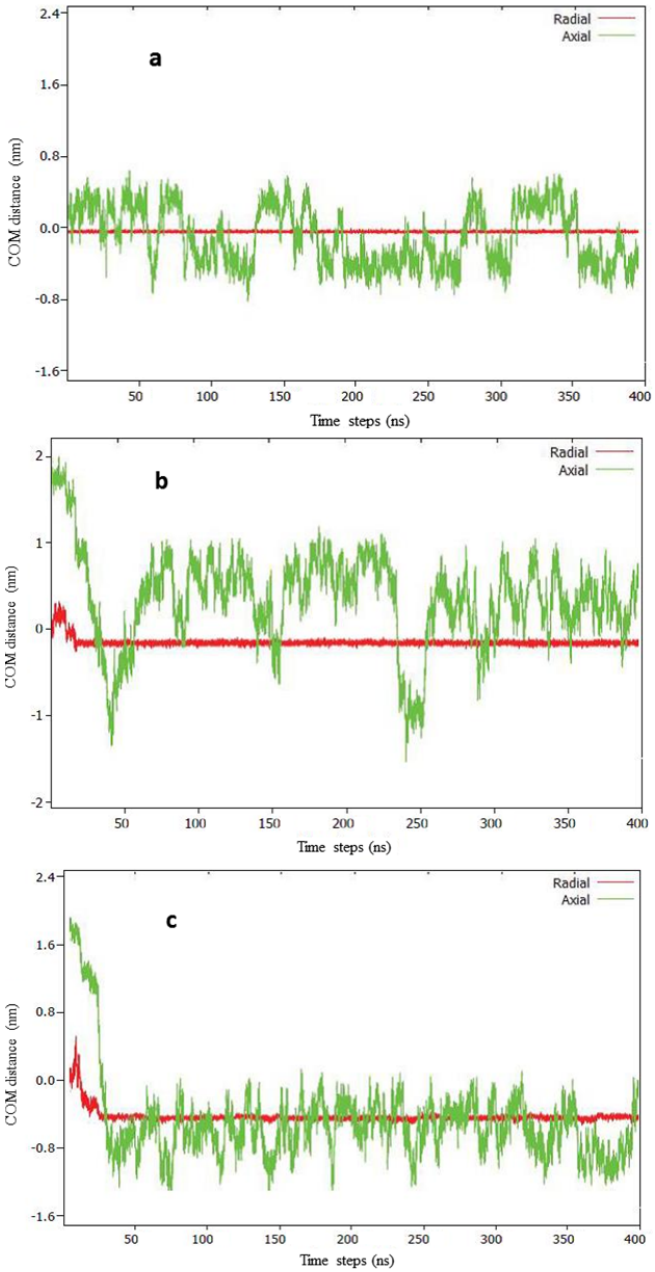

Fig. 5 (a) Normalized COM distance the drug and the cell membrane (b) Normalized COM distance between the nanocarrier and the cell membrane (c) Normalized COM distance between the drug and the nanocarrier

IV. Discussion

Using MDS, we examined van der Waals energy between (a) paclitaxel and cell membrane, (b) paclitaxel and the nanocarrier and also (c) the nanocarrier and cell membrane using Newton's Law of Motion as shown in Figs. 4 (a), (b) and (c), respectively. Van der Waals energy represents electrical action and reaction between atoms and molecules which are close to each other. There is a sharp drop after 20 ns in Fig. 4 (c) in comparison with two others which illustrate the decreasing of energy between the carrier and the cell membrane as they close to each other; therefore they express favorable interaction and bio stability. In Fig. 4 (a), the anti-cancer drug paclitaxel interact suitably with the cell membrane to affect the targeted cancer cell based on the loss of the energy level. Moreover, in this graph, the decreasing of energy profile has been observed; however, the decline level of energy is lower than the nanocarrier and cell membrane interaction energy graph, besides, more fluctuations can be observed which show less stability and adsorption. Furthermore, Fig. 4 (b) shows the interaction energy of the paclitaxel and DPPC. It indicates that the hydrophobic anti-cancer drug paclitaxel can bind within the phospholipid nanocarrier DPPC comprehensively in order to transfer to the targeted tumor. The observation of drug and the nanocarrier's behavior and their favorable stability in our computational study confirms Peetla's experimental observations. Peetla et al. analyzed the penetration of anti-cancer drug paclitaxel across the DPPC monolayer, while in this study, the DPPC was considered as a nanocarrier which would interact and encapsulate the paclitaxel [21].

This study investigated the van der Waals energy interaction between (a) the anti-cancer drug and cell membrane and (b) the encapsulated drug within phospholipid nanocarrier and cell membrane, that in previous computational studies it has not been studied. The major objective was to show that the encapsulated drug can be much more effective than individual drug due to the extended adsorption duration in the cell membrane's surface. In addition, the drug and the nanocarrier behavior in junction to each other from the interaction energy point of view was studied. For example, Peetla et al. investigated the drug delivery systems experimentally and showed that a carrier close to the targeted cell behaves favorably by atomic force microscopy (AFM) method [21]; we performed van der Waals energy interactions in the drug delivery system by using MDS and also concluded that the efficacy and stability of the encapsulated drug is impressive. Salas et al. computationally studied the interaction of dendrimer as a carrier with an anti-inflammation drug. They showed that the drug and the dendrimer represent the suitable interaction with each other [22]. Dai et al. carried out a MDS study by utilizing different concentration of Borneol as a natural penetration enhancer to investigate its interaction with the DPPC, by considering temperature effects [26]. They significantly found that increasing of concentration and temperature within a limited variation could promote and increase the penetration property of borneol. It was found that the thinning and growth effects of this drug on the DPPC membrane may be helpful for improving the penetration of lipophilic drugs. They discussed just two parameters including concentration and temperature, for interaction analyses between drug and DPPC in comparison with our

investigations. Also, Jambeck et al. analyzed the interaction between photosensitizing drug and liposome as a carrier. They considered liposome model with over 2500 lipids, and investigated its interaction with different concentrations of hypericin as a natural drug in 10 microsecond simulations. They found that according to experimental works, by increasing the degree of hypericin, liposomes expand, but interestingly, no major structural differences happened. In comparison to our work, Jambeck's group reported the distribution and orientations of the hypericins within the lipid bilayer, and the potential of mean force to shift a hypericin molecule from the interior aqueous "droplet" through the liposome bilayer, but they focused only on the carrier and drug interaction and behavior [23]. Not only we confirmed previous observations, but also we studied three systems and compared them with each other which prove our much more comprehensive study. Although Jambeck et al. examined the drug and the carrier interaction properly, we extended our computational assessment to the (a) free drug with cell membrane and also (b) encapsulated drug with cell membrane.

The value of interaction energy's deviation for three systems approved the higher efficiency of the nanocarrier in comparison to the free drug in the cell membrane surface. The RMSD value lower than 1 angstrom shows exact converges and adequate interaction, therefore the drug would be encapsulated completely within the nanocarrier from the interaction energy point of view as the RMSD value was 0.91 angstrom. According to the RMSD value, the nano-carrier showed higher interaction with cell membrane (RMSD value: 0.95 angstrom) in compare to the anticancer drug interaction with cell membrane (RMSD value: 1.18 angstrom).

Additionally, normalized COM distance or "center of gravity" between the drug and the cell membrane as well as between the nanocarrier and cell membrane were studied in order to computationally investigate the molecular dynamic process of the free drug and the encapsulated within the nanocarrier with the aim of comparing their efficacy. The simulation was done during 400 ns and plotted in Figs. 5 (a) and (b), respectively. COM is defined as a uniform gravity field to express the unique point in a system. It is obvious that COM is not fixed on specific amount. However, the amount of fluctuation presented in COM provides information about two components' adsorption and stability next to each other and also how effective their interaction is.

In the current study, Fig. 5 (b) shows that the amount of COM in the interaction system of the encapsulated drug by the nanocarrier with the cell membrane is smaller than the interaction system of the drug with the cell membrane. Therefore, the interaction and molecular adsorption of the nanocarrier to the cell membrane is more favorable and stable. This system is more efficient than utilizing the drug individually. Moreover, the interaction and junction of the hydrophobic anti-cancer drug paclitaxel with the phospholipid nanocarrier is investigated (Fig. 5 (c)). The COM between the drug and the nanocarrier is decreased that expresses their suitable junction and favorable interaction during transporting to the targeted tumor cell. Outcomes represent that the phospholipid nanocarriers could be the best alternative in order to transport hydrophobic drugs to the targeted point in the body environment.

Computer simulations have emerged as an extremely valuable tool to determine and visualize the molecular interaction of the drug and the nanocarrier with the bio-membrane, due to affordability and time consumption in obtaining actual experimental data for such systems. Simulations by Kang et al., using molecular dynamics, showed the COM in relation to anti-cancer drug transferring through the cell membrane. They understood that the PTX concentration is a critical factor for its distribution of as a hydrophobic drug in the cell membrane through the free energy calculation. They discovered that in a desired concentration of PTX, the free energy moves towards to the core of membrane which is hydrophobic, and central barrier forces decrease. So, the hydrophobicity of drug components matches the local position of the cell membrane [24]. In compression to our study they related the COM to the interaction energy and coordination number, while in this study the COM was analyzed individually. Cheng et al. studied the adsorption and mobility of peptides in nanotubes by simulation [25], but based on outcomes and findings presented herein, we aim to perform the interaction quality by using van der Waals energy and normalized COM in the three systems, the drug and the nanocarrier, the drug and the cell membrane and finally the nanocarrier and the cell membrane.

A few computational studies have been used to examine molecular-scale circumstances that occur between the encapsulated drug within a nanocarrier and the cell membrane [28], [49]-[52]. COM in this system would show the higher tendency of the nanocarrier to adsorb to the cell membrane in comparison with the drug and the cell membrane interaction system. In this study, not only we approved the previous experimental [27]-[29] and computational studies [28], [49]-[52] of the drug and the nanocarrier system's interactions, but also we demonstrated better interaction and efficacy in junction of the nanocarrier to the cell membrane.

To prove reliability of results of this study, the value of COM deviation for three systems was calculated which demonstrated that RMSD value of the drug with the nanocarrier is 0.92 angstrom, thus the drug interacted properly with the nanocarrier in order to transport to the targeted cell. COM analysis of the nanocarrier with the cell membrane had higher accuracy by the RMSD value of 0.92 angstrom to the anti-cancer drug interaction with the cell membrane with RMSD value of 1.23 angstrom.

The results achieved in this study are in accordance with the former experiments and computational analyses that derived suitable coupling was shown in PTX and DPPC nanocarrier interaction [22]-[25], [27]-[29], [49], [51], [52]. In the other words, the nanocarrier encapsulates the anti-cancer drug favorably to transport the drug to the targeted point in the human body. As a summary, this molecular dynamics computational analysis allowed us to evaluate drug delivery systems without consuming significant time and cost.

V. Conclusion

Herein, atomic simulations of PTX as a hydrophobic anticancer drug and DPPC as a drug nanocarrier were carried out in interaction with the cell membrane using molecular dynamic simulation in order to assess the van der Waals energy and COM. The drawn energy profile reveals that the absorption and the interaction of the nanocarrier in the cell membrane's interface are better than the interaction of the drug individually with the cell membrane, resulting in a more favorable interaction and biostability of DPPC, the phospholipid nanocarrier. Moreover, it was demonstrated that PTX embedded and interacted suitably with DPPC through decreasing of their interaction energy. Furthermore, the modeling studies discussed here provided remarkable insight into the fundamental mechanisms of drug-nanocarrier, drug-cell membrane and nanocarrier-cell membrane interaction in human body. Notably, the obtained results showed that COM, reflecting the gravity between systems molecules is one of the most important factors in binding of two parts in the systems and must be carefully incorporated in drug delivery analysis. Generally, when the distance between two components decrease and remain approximately constant in the simulated systems, the binding and adsorption takes place. As a result, the better binding and stable junction of the nanocarrier and the cell membrane in comparison with the system of the drug and the cell membrane has been shown. A better understanding of the interactions between hydrophobic drugs individually or by utilizing nanocarriers and cell membranes at a molecular level will help in designing more efficient drug delivery systems.

Conflict of Interest

The authors have declared no conflict of interest.

List of abbreviations

DPPC: Dipalmitoylphosphatidylcholine
COM: Center of mass
MD: Molecular dynamics
MDS: Molecular dynamics simulation
PDB: Protein data bank
RMSD: Root-mean-square deviation
RMSE: Root-mean-square error
AFM: Atomic force microscopy
PTX: Paclitaxel

References

[1] Shi, J., et al., *Nanotechnology in drug delivery and tissue engineering: from discovery to applications.* Nano letters, 2010. 10(9): p. 3223-3230.
[2] Gupta, U., et al., *A review of in vitro–in vivo investigations on dendrimers: the novel nanoscopic drug carriers.* Nanomedicine: Nanotechnology, Biology and Medicine, 2006. 2(2): p. 66-73.
[3] Svenson, S., *Dendrimers as versatile platform in drug delivery applications.* European Journal of Pharmaceutics and Biopharmaceutics, 2009. 71(3): p. 445-462.
[4] Herce, H.D. and A.E. Garcia, *Molecular dynamics simulations suggest a mechanism for translocation of the HIV-1 TAT peptide across lipid membranes.* Proceedings of the National Academy of Sciences, 2007. 104(52): p. 20805-20810.
[5] Schiff, P.B., J. Fant, and S.B. Horwitz, *Promotion of microtubule assembly in vitro by taxol.* 1979.
[6] Jordan, M.A. and L. Wilson, *Microtubules as a target for anticancer drugs.* Nature Reviews Cancer, 2004. 4(4): p. 253-265.
[7] Amos, L.A. *What tubulin drugs tell us about microtubule structure and dynamics*. in *Seminars in cell & developmental biology*. 2011. Elsevier.
[8] Löwe, J., et al., *Refined structure of αβ-tubulin at 3.5 Å resolution.* Journal of molecular biology, 2001. 313(5): p. 1045-1057.
[9] Mastropaolo, D., et al., *Crystal and molecular structure of paclitaxel (taxol).* Proceedings of the National Academy of Sciences, 1995. 92(15): p. 6920-6924.
[10] Balasubramanian, S.V., J.L. Alderfer, and R.M. Straubinger, *Solvent- and concentration-dependent molecular interactions of taxol (paclitaxel).* Journal of pharmaceutical sciences, 1994. 83(10): p. 1470-1476.
[11] Koudelka, Š. and J. Turánek, *Liposomal paclitaxel formulations.* Journal of Controlled Release, 2012. 163(3): p. 322-334.
[12] Zhang, Z., L. Mei, and S.-S. Feng, *Paclitaxel drug delivery systems.* Expert opinion on drug delivery, 2013. 10(3): p. 325-340.
[13] Gao, Y., et al., *Enzyme-instructed molecular self-assembly confers nanofibers and a supramolecular hydrogel of taxol derivative.* Journal of the American Chemical Society, 2009. 131(38): p. 13576-13577.
[14] Gratton, S.E., et al., *The effect of particle design on cellular internalization pathways.* Proceedings of the National Academy of Sciences, 2008. 105(33): p. 11613-11618.
[15] Loverde, S.M., et al., *Curvature, rigidity, and pattern formation in functional polymer micelles and vesicles–From dynamic visualization to molecular simulation.* Current Opinion in Solid State and Materials Science, 2011. 15(6): p. 277-284.
[16] Loverde, S.M., M.L. Klein, and D.E. Discher, *Nanoparticle Shape Improves Delivery: Rational Coarse Grain Molecular Dynamics (rCG-MD) of Taxol in Worm-Like PEG-PCL Micelles.* Advanced materials, 2012. 24(28): p. 3823-3830.
[17] Kopeć, W., J. Telenius, and H. Khandelia, *Molecular dynamics simulations of the interactions of medicinal plant extracts and drugs with lipid bilayer membranes.* FEBS Journal, 2013. 280(12): p. 2785-2805.
[18] Loverde, S.M., *Molecular simulation of the transport of drugs across model membranes.* The Journal of Physical Chemistry Letters, 2014. 5(10): p. 1659-1665.
[19] Abu-Surrah, A.S. and M. Kettunen, *Platinum group antitumor chemistry: design and development of new anticancer drugs complementary to cisplatin.* Current medicinal chemistry, 2006. 13(11): p. 1337-1357.
[20] Dezhampanah, H., A.K. Bordbar, and S. Farshad, *Thermodynamic characterization of phthalocyanine–human serum albumin interaction.* Journal of Spectroscopy, 2011. 25(5): p. 235-242.
[21] Peetla, C., A. Stine, and V. Labhasetwar, *Biophysical interactions with model lipid membranes: applications in drug discovery and drug delivery.* Molecular pharmaceutics, 2009. 6(5): p. 1264-1276.
[22] Avila-Salas, F.n., et al., *Study of interaction energies between the PAMAM dendrimer and nonsteroidal anti-inflammatory drug using a distributed computational strategy and experimental analysis by ESI-MS/MS.* The Journal of Physical Chemistry B, 2012. 116(7): p. 2031-2039.
[23] Jämbeck, J.P., et al., *Molecular Dynamics Studies of Liposomes as Carriers for Photosensitizing Drugs: Development, Validation, and Simulations with a Coarse-Grained Model.* Journal of Chemical Theory and Computation, 2014. 10(1): p. 5-13.
[24] Kang, M. and S.M. Loverde, *Molecular simulation of the concentration-dependent interaction of hydrophobic drugs with model cellular membranes.* The Journal of Physical Chemistry B, 2014. 118(41): p. 11965-11972.
[25] Cheng, Y., Q.X. Pei, and H. Gao, *Molecular-dynamics studies of competitive replacement in peptide–nanotube assembly for control of drug release.* Nanotechnology, 2009. 20(14): p. 145101.
[26] Dai, X., et al., *Effects of Concentrations on the Transdermal Permeation Enhancing Mechanisms of Borneol: A Coarse-Grained Molecular Dynamics Simulation on Mixed-Bilayer Membranes.* International Journal of Molecular Sciences, 2016. 17(8): p. 1349.
[27] Allen, T.M. and P.R. Cullis, *Drug delivery systems: entering the mainstream.* Science, 2004. 303(5665): p. 1818-1822.
[28] Discher, D.E., et al., *Emerging applications of polymersomes in delivery: from molecular dynamics to shrinkage of tumors.* Progress in polymer science, 2007. 32(8): p. 838-857.
[29] Maruyama, K., *Intracellular targeting delivery of liposomal drugs to*

solid tumors based on EPR effects. Advanced drug delivery reviews, 2011. 63(3): p. 161-169.
[30] Maeda, H., T. Sawa, and T. Konno, *Mechanism of tumor-targeted delivery of macromolecular drugs, including the EPR effect in solid tumor and clinical overview of the prototype polymeric drug SMANCS.* Journal of controlled release, 2001. 74(1): p. 47-61.
[31] Danhier, F., O. Feron, and V. Préat, *To exploit the tumor microenvironment: passive and active tumor targeting of nanocarriers for anti-cancer drug delivery.* Journal of Controlled Release, 2010. 148(2): p. 135-146.
[32] Maeda, H., H. Nakamura, and J. Fang, *The EPR effect for macromolecular drug delivery to solid tumors: Improvement of tumor uptake, lowering of systemic toxicity, and distinct tumor imaging in vivo.* Advanced drug delivery reviews, 2013. 65(1): p. 71-79.
[33] Yagi, K., et al., *Basic study on gene therapy of human malignant glioma by use of the cationic multilamellar liposome-entrapped human interferon beta gene.* Human gene therapy, 1999. 10(12): p. 1975-1982.
[34] Humphrey, W., A. Dalke, and K. Schulten, *VMD: visual molecular dynamics.* Journal of molecular graphics, 1996. 14(1): p. 33-38.
[35] Brooks, B.R., et al., *CHARMM: the biomolecular simulation program.* Journal of computational chemistry, 2009. 30(10): p. 1545-1614.
[36] Karplus, M., *CHARMM: A program for macromolecular energy, minimization, and dynamics calculations.* J Comput Chem, 1983. 4: p. 187217.
[37] Klauda, J.B., et al., *Update of the CHARMM all-atom additive force field for lipids: validation on six lipid types.* The journal of physical chemistry. B, 2010. 114(23): p. 7830.
[38] Vanommeslaeghe, K., et al., *CHARMM general force field: A force field for drug-like molecules compatible with the CHARMM all-atom additive biological force fields.* Journal of computational chemistry, 2010. 31(4): p. 671-690.
[39] Panczyk, T., et al., *Sidewall Functionalization of Carbon Nanotubes as a Method of Controlling Structural Transformations of the Magnetically Triggered Nanocontainer: A Molecular Dynamics Study.* The Journal of Physical Chemistry C, 2015. 119(15): p. 8373-8381.
[40] Xing, Y.-F., et al., *Dynamic Mechanism of Single-Stranded DNA Encapsulated into Single-Wall Carbon Nanotubes: A Molecular Dynamics Simulation Study.* Journal of the Physical Society of Japan, 2014. 83(2): p. 024801.
[41] Jiang, W., et al., *Generalized scalable multiple copy algorithms for molecular dynamics simulations in NAMD.* Computer physics communications, 2014. 185(3): p. 908-916.
[42] Rapaport, D.C., *The art of molecular dynamics simulation*. 2004: Cambridge university press.
[43] Klauda, J.B., et al., *Improving the CHARMM force field for polyunsaturated fatty acid chains.* The Journal of Physical Chemistry B, 2012. 116(31): p. 9424-9431.
[44] Mitra, A. and D. Sept, *Taxol allosterically alters the dynamics of the tubulin dimer and increases the flexibility of microtubules.* Biophysical journal, 2008. 95(7): p. 3252-3258.
[45] Phillips, J.C., et al., *Scalable molecular dynamics with NAMD.* Journal of computational chemistry, 2005. 26(16): p. 1781-1802.
[46] Frenkel, D. and B. Smit, *Understanding molecular simulation: from algorithms to applications.* Computational sciences series, 2002. 1: p. 1-638.
[47] Schreiner, W., et al., *Relaxation Estimation of RMSD in Molecular Dynamics Immunosimulations.* Computational and mathematical methods in medicine, 2012. 2012.
[48] Schieborr, U., et al., *MOTOR: Model assisted software for NMR structure determination.* Proteins: Structure, Function, and Bioinformatics, 2013. 81(11): p. 2007-2022.
[49] He, X., et al., *Molecular analysis of interactions between a PAMAM dendrimer–paclitaxel conjugate and a biomembrane.* Physical Chemistry Chemical Physics, 2015. 17(44): p. 29507-29517.
[50] Lin, X., et al., *Promote potential applications of nanoparticles as respiratory drug carrier: insights from molecular dynamics simulations.* Nanoscale, 2014. 6(5): p. 2759-2767.
[51] Mousavi, S.Z., et al., *Carbon nanotube-encapsulated drug penetration through the cell membrane: an investigation based on steered molecular dynamics simulation.* The Journal of membrane biology, 2013. 246(9): p. 697-704.
[52] Bunker, A., *Poly (ethylene glycol) in drug delivery, why does it work, and can we do better? All atom molecular dynamics simulation provides some answers.* Physics Procedia, 2012. 34: p. 24-33.