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Teaser The carbon-nanotube-based target-specific delivery of drugs, or other molecular cargo, has emerged as one of the most promising biomedical applications of nanotechnology to circumvent the limitations associated with the clinically available various nonspecific therapeutic agents.

Molecular dynamics simulation strategies for designing carbon-nanotube-based targeted drug delivery

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The carbon nanotube (CNT)-based target-specific delivery of drugs, or other molecular cargo, has emerged as one of the most promising biomedical applications of nanotechnology. To achieve efficient CNT-based drug delivery, the interactions between the drug, CNT and biomolecular target need to be properly optimized. Recent advances in the computer-aided molecular design tools, in particular molecular dynamics (MD) simulation studies, offer an appropriate low-cost approach for such optimization. This review highlights the various potential MD approaches for the simulation of CNT interactions with cell membranes while emphasizing various methods of cellular internalization and toxicities of CNTs to build new strategies for designing rational CNT-based targeted drug delivery to circumvent the limitations associated with the various clinically available nonspecific therapeutic agents.

Introduction

The target-specific delivery of drugs or other molecular cargo by using carbon nanotubes (CNTs) has emerged as one of the most promising biomedical applications of nanotechnology [1,2]. The ability of functionalized CNTs to become ingested into specifically targeted cells to release their contents in response has created a substantial impact for the treatment of patients suffering from various diseases [3]. In particular, CNT-based targeted drug delivery has gained much attention for the improvement of cancer treatment to circumvent the unwanted side-effects associated with nonspecific chemotherapy, which tends to kill normal healthy cells as well [4,5]. Several research articles, reviews and books have been published highlighting the various insights based on experimental investigations on the biocompatibility, toxicity, functionalization, loading, unloading and cellular uptake of CNTs [6–11]. However, the remarkable physical, chemical and mechanical properties of CNTs enable them to be useful for the applications of various drugs and proteins, as well as gene delivery [3,5].

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One of the key advantages of CNT-based target-specific drug delivery is that a highly toxic drug can be used at a lower dosage thus reducing side-effects [6,8]. Moreover, CNTs provide the perfect isolated environment for the drug while protecting it from degradation and reaction with healthy cells as well as allowing the drug to circulate for a long period in the blood until it reaches and is delivered to the target site with minimal side-effects. Thus, CNT-based drug delivery offers a promising alternative for the treatment of various diseases such as infections, metabolic diseases and autoimmune diseases, as well as for use in gene therapy [3,4,12]. Recent advances in computer-aided drug design (CADD) strategies provide a great opportunity to efficiently build and simulate (*in silico*) the interactions of CNTs with drugs as well as cell membranes to gain insight into the various physicochemical requirements for engineering effective site-directed CNT-based drug delivery [13–15].

This review covers the physical and surface properties of CNT structure that affect interactions with drugs and biomolecules. Various mechanisms and the factors affecting internalization of CNTs within the cell membrane are also described. Among the various CADD strategies, molecular dynamics (MD) simulation is the most common approach to gain insight into the CNT interaction with biomolecules including cell membranes [13–15]. However, owing to the huge size of the CNT molecular system, several approaches that were developed to reduce the degrees of freedom and to simplify the intermolecular interactions are also emphasized here.

Structural properties and functionalization of carbon nanotubes

Carbon nanotubes are cylindrical wrapped graphene sheets of hexagonally arranged sp^2-hybridized carbon atoms. They exist as a single cylinder known as single-walled carbon nanotubes (SWCNTs) and multi-cylinders with coincided centers known as multiwalled carbon nanotubes (MWCNTs). The SWCNTs have diameter ranges 0.4–3.0 nm and length 20–1000 nm, whereas MWCNTs have an average central cylindrical tube diameter of 1–3 nm and external cylindrical tube diameter of 2–100 nm with length varying from one to several micrometers (Fig. 1a) [4]. Based on the arrangement of the graphite layer, MWCNTs can be categorized into two types: 'parchment-like' structures consisting of a graphene sheet rolled up around itself and 'Russian doll' models

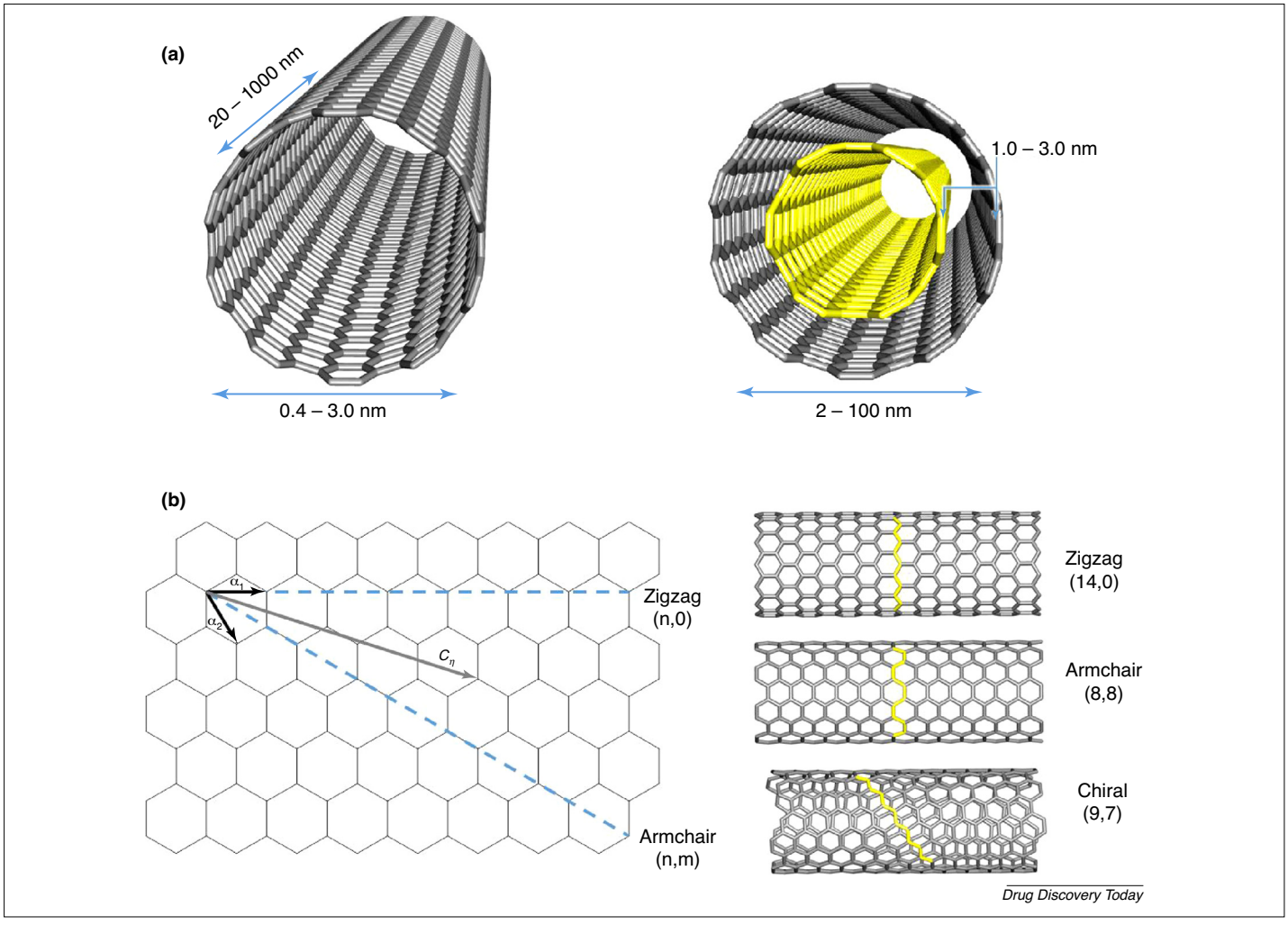

FIGURE 1

(a) The dimensions of a single-walled carbon nanotube (SWCNT) on the left and multiwalled carbon nanotube (MWCNT) on the right. **(b)** Schematic representation of graphene sheet showing zigzag and armchair configurations (represented as dashed lines). Any arbitrary configuration represented by C_h vector can be made by summation of integer multiplicand of a_1 and a_2a2 vectors.

with multiple graphene sheets arranged within a concentric structure [16]. Another important physical property of CNTs, in particular for SWCNTs, is chirality which represents the axis around which the graphene plane is wrapped. The two main configurations of CNTs are zigzag and armchair; and several sub-configurations can be obtained by shifting the wrapping axis from the zigzag plane toward the armchair plane (Fig. 1b) [17]. Therefore, chirality can be simply represented as n and m indices. Knowing the indices for a CNT, it is possible to deduce other parameters like diameter and chiral angle as shown in Eqs (1) and (2) [1]. The influence of thickness, diameter and chirality on the elastic properties of CNTs is properly explained by Tserpes and Papanikos [18].

$$d = \frac{a}{\pi}\left(n^2 + nm + m^2\right)^{1/2} \quad (1)$$

$$\theta = \tan^{-1}\left(\sqrt{3}m/(m+n)\right) \quad (2)$$

CNTs are mainly synthesized by following three standard techniques such as chemical vapour deposition (CVD), arc discharge and laser ablation [19]. The former method is conducted at comparatively low temperature (<800 °C), whereas the latter two methods require high temperature (>1700 °C). Certain non-standard methods such as pyrolysis and hydrothermal treatment have also been used for the synthesis of CNTs.

The surface of CNTs in their original form (pristine CNTs) is a 'bald' one. Pristine CNTs are highly hydrophobic and cannot be directly introduced to the human body because that could lead to various undesirable and severe toxicities including cell-cycle arrest, apoptosis and necrosis [20]. Therefore, the functionalization of the CNT surface is of paramount importance before exposing them to the biological environment [21]. Functionalization of CNTs helps to increase the aqueous solubility, dispersion and efficacy of insoluble drugs as well as to improve the biocompatibility to reduce the nonspecific interaction with cell membranes and related toxicities. Functionalization is carried out by either covalent or noncovalent bonding of different functional groups on the surface or at the open ends of CNTs (Fig. 2) depending upon specific application [11].

There are various chemical reactions involved in the covalent functionalization of CNTs such as oxidation, hydrogenation, amidation, halogenation (F/Cl/Br), thiolation (SH) and addition of carbenes or nitrene [12]. An example of covalent functionalization is the oxidation of the CNT surface to produce –COOH functional groups that can be used to link other molecules by amidation or esterification [16]. Covalent functionalization results in altered hybridization from sp^2 to sp^3 on carbon atoms of CNTs, simultaneously blocking the π-electron transition which is found to be favorable for pharmaceutical drug delivery because it causes slow release of therapeutic agents [12]. Hence, covalent functionalized CNTs are considered to be most promising for diagnosis and pharmaceutical drug delivery. It is worth mentioning that the damage of the π-network is a big concern for fluorescence imaging applications because it shows a detrimental effect on fluorescence quantum efficiency.

Noncovalent functionalization of CNTs mainly includes supramolecular adhesion of polymers, biomolecules or amphiphilic surfactants on the CNT surface through van der Waals, pi–pi (π–π) or hydrophobic interactions [1]. Noncovalent functionalization can also significantly enhance the solubility and dispersibility of CNTs but, in contrast to covalent functionalization, it has limited capability of drug delivery owing to the presence of weak van der Waals forces. The functionalized CNTs have been efficiently used to deliver proteins, nucleic acids and small drug molecules inside the cell-specific targets [3,12].

Recent advances in computer modeling approaches, in particular MD simulation, significantly help to investigate the physicochemical properties required for the functionalization and improving solubility, as well as gaining insight into the adsorption mechanisms of various drugs on pristine as well as functionalized CNTs. For example, Arsawang *et al.* investigated the structural properties required for encapsulation of an anticancer drug gemcitabine in SWCNTs by employing MD simulation and found that the drug molecule preferred to reside inside the SWCNTs by forming π-stacking interactions between the CNTs and the cytosine ring of the drug [23]. Similarly, Hashemzadeh and Raissi performed MD simulation to compare and gain insight into the adsorption mechanism of the anticancer drug paclitaxel (PTX) on pristine and three types of functionalized CNTs [24]. Functionalization of CNTs was carried out by using polyethylene glycol (PEG), carboxylic (COOH) and amine (CH_2NH_2) groups. The

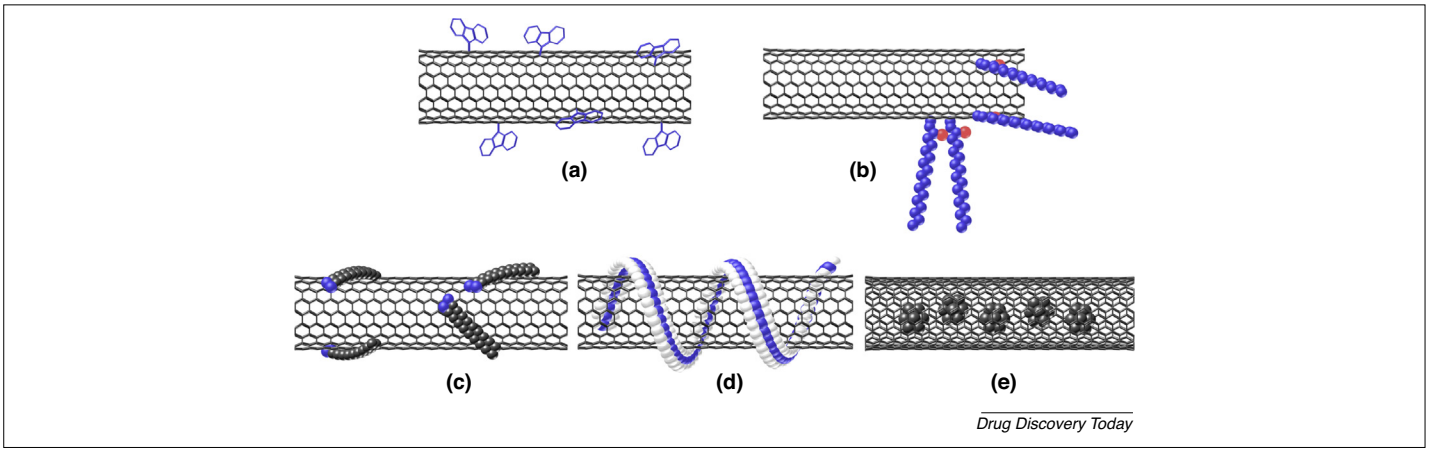

FIGURE 2

Functionalization of carbon nanotubes (CNTs) by covalent linkages either **(a)** at the defects and open ends or **(b)** on the side wall. The noncovalent functionalization includes adsorption of **(c)** surface active agents, **(d)** polymers or even **(e)** insertion of small molecules within the CNT [22].

results showed that PTX adsorbed on pristine CNTs by forming π–π interactions, whereas the maximum adsorption of PTX took place on the surface of PEG-CNTs by forming more-polar interactions as compared with other functionalized CNTs. Moreover, the PEG-CNT system also showed the highest aqueous solubility by forming polar intermolecular H-bonds. There are many such examples of successful exploration of computer modeling of CNTs reported in the literature indicating its potential for the design and optimization of various parameters required for the functionalization as well as improvement of pharmacokinetic properties to enhance the biocompatibility while reducing the toxicity of CNTs.

Interactions of carbon nanotubes with the cell membrane

One of the major concerns in the development of nanoparticle (NP)-based drug delivery is to ensure their capability to interact and penetrate the biological membranes successfully. To predict the CNT-based drug delivery at the cellular level, the interaction between the cargo CNT and the cell membrane needs to be studied. Several mechanisms were proposed and experimentally approved for the cellular internalization of CNTs. It is important to note that some internalized CNTs can also lead to toxic effects on the cells owing to their high reactivity as well as various other incompatible surface chemistries, as evident mainly from the cellular interaction of pristine CNTs [25]. Therefore, the parameters governing the cellular internalization of CNTs should be accurately optimized during the design process to achieve efficient and selective drug delivery.

Mechanisms of internalization of carbon nanotubes by the cell membrane

CNTs can be administered into the human body by various methods such as oral, intravenous (IV), transdermal, subcutaneous, intraperitoneal injection and inhalation routes. Cellular internalization of CNTs is related to several factors such as surface characteristics, interactions with the medium and biomolecules. The surface properties of importance include chemical composition, roughness, functionalization, shape, porosity, surface crystallinity, heterogeneity, the angle of curvature and hydrophobicity or hydrophilicity [25]. Experimentally, it has been suggested that pristine CNTs can be internalized within cells either by endocytosis or spontaneous insertion and diffusion across the cell membrane. It is important to note that CNT internalization is not completely dependent on surface functionality [26]. Several mechanisms of internalization of CNTs by cell membranes have been proposed (Fig. 3).

Direct penetration or nanopenetration

This is an energy-independent passive process of CNT internalization either through membrane-transport-protein channels or pores or directly through the cell membrane. Direct penetration offers the advantage of avoiding endosomal entrapment and the potential for lysosomal degradation [27,28]. It has been postulated that energy-independent cellular internalization of CNTs is similar to passive diffusion of nano-needles and also similar to the process of polycationic cell-penetrating peptides (CPPs). In this regard, a study of passive penetration of fluorescein-isothiocyanate-linked CNTs and G-protein-coupled CNTs into keratinocytes and fibroblasts, respectively, suggests that functionalized CNTs resembling the morphology of CPPs and possessing overall charge might prefer to undergo penetration to the cellular membrane rather than endocytosis [29].

Endocytosis

Endocytosis is one of the most common methods for cellular internalization of functionalized CNTs by energy-dependent active transport in which the cytoplasmic membrane engulfs them by enclosing them in vesicles or vacuoles inside the cell [27,28]. It is worth mentioning that this process of energy-dependent endocytosis might be hindered at low temperature, as well as in a low ATP environment [30]. Internalization of CNTs within the cell by

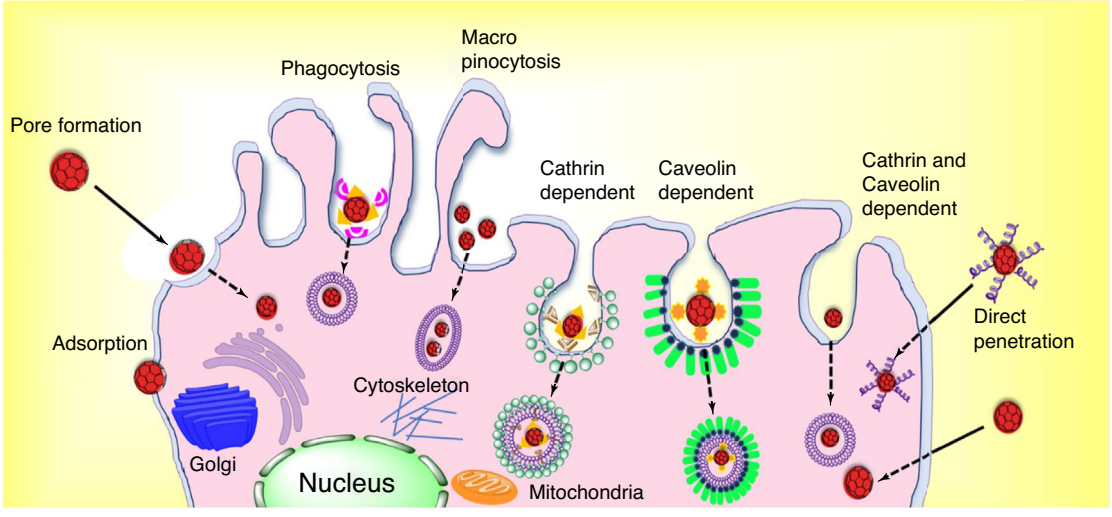

FIGURE 3

Schematic representation of the nanoparticle–biomembrane interaction mechanism. Four mechanisms, including adsorption onto the membrane surface, pore formation, direct penetration and endocytosis, are involved in nanoparticle–biomembrane internalization. Reprinted, with permission, from Ref. [28].

the formation of endosomes can lead to lysosomal degradation of the CNT delivery system [31]. Occasionally, the cargo CNT can escape from the endosomal trap by pore formation, proton sponge effect or fusion in the endosomal membrane [32]. The endocytosis process follows different mechanisms that often involve interaction with membrane receptors (Fig. 4).

Clathrin-mediated endocytosis (< 300 nm) is the most important route for internalization of NPs inside the cells (even exploited for uptake of pathogens like viruses and bacteria). In this method of internalization, transmembrane receptors undergo sorting upon binding to their extracellular ligand. The sorted receptors activate the formation of 'coated pits' due to assembly of several cytoplasmic proteins leading to the formation of a clathrin cage (Fig. 5). This energy-dependent clathrin-mediated endocytosis (CME) is also known as receptor-mediated endocytosis (RME). This process can facilitate the endocytosis of positively charged (e.g., plain gold) and negatively charged (e.g., PEG-coated gold) NPs [25,33].

Caveolae-mediated endocytosis (<80 nm) is used for cell signaling, vesicular transport, as well as for virus entry. Caveolae are membrane invaginations 50–80 nm in size, containing the cholesterol-binding protein caveolin and sphingolipids [34]. Caveolae-mediated endocytosis also plays an important part in the cellular uptake of positively and negatively charged NPs, particularly in endothelial cells [25].

Macropinocytosis (>200 nm) is a process where the cellular internalization takes place by the formation of waving sheet-like extensions of the plasma membrane due to actin-regulated movement. The mechanism most probably involves no interactions with transmembrane proteins. Macropinocytosis is found to play an important part in the cellular uptake of mainly positively charged NPs like plain gold NPs [35].

Phagocytosis (>750 nm) is a process of cellular internalization that is only performed by specialized cells like immune cells (monocytes, macrophages and neutrophils) to engulf huge particles with diameter >750 nm such as pathogens, dead cells and

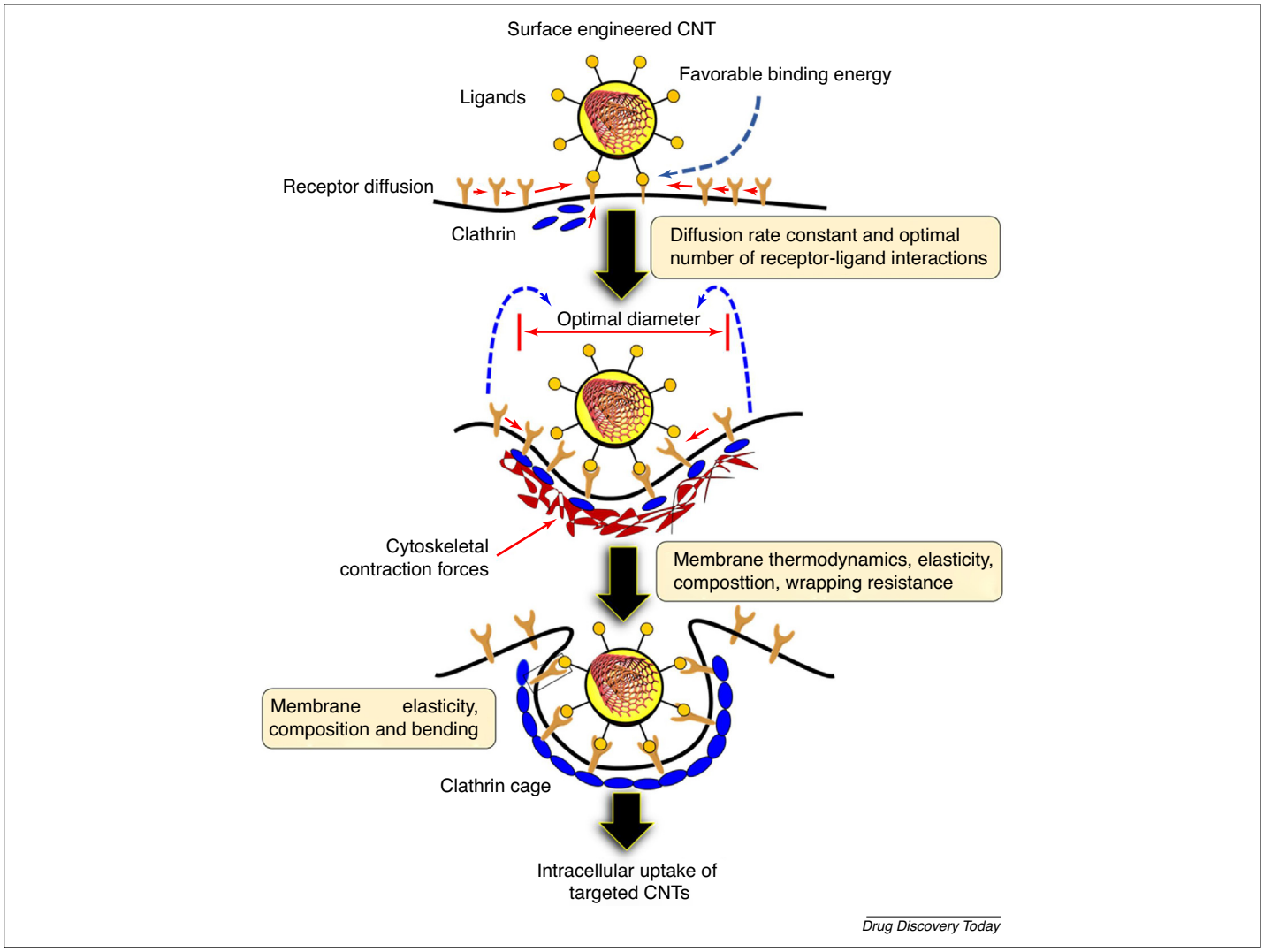

FIGURE 4

Scheme showing nanoparticle wrapping at the cellular surface membrane. The particle uptake starts with binding to the membrane through specific (ligand–receptor) or nonspecific (for example hydrophobic, Coulombic) interactions. The interactions should be strong enough (decrease free energy of the system) to overcome resistive forces (such as membrane bending). The blue beads represent clathrin, an example of an endocytic component that engages in the energy-dependent uptake of the particle through interaction between ligands (yellow dots) on the particle surface and membrane receptors (Y-shaped).

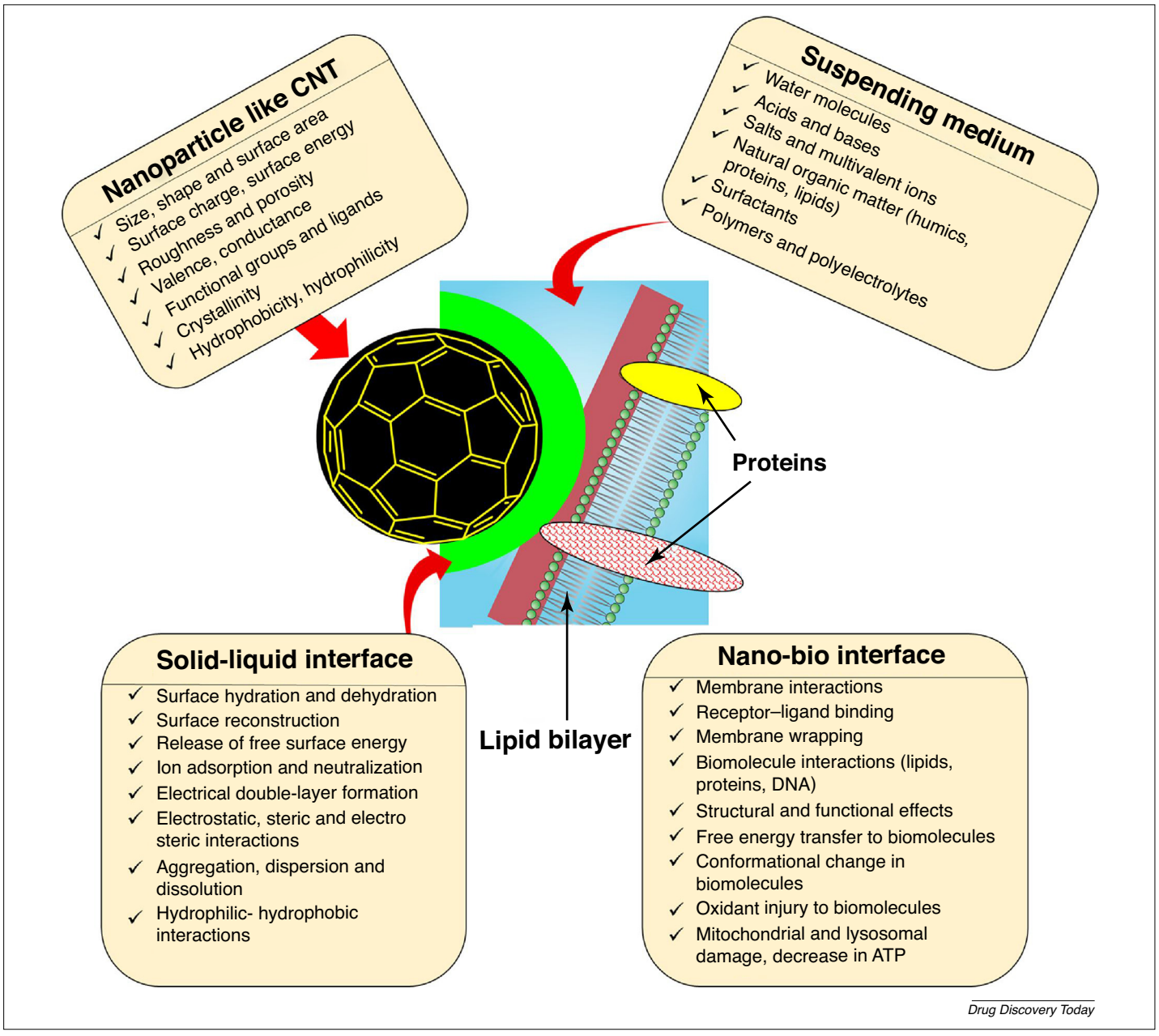

FIGURE 5

Representation of the interface between a nanoparticle and a lipid bilayer. The factors that affect the nanoparticle internalization belong to the nanoparticle surface, suspending medium and the dynamic interactions between the solid–liquid interface and the biomolecules and cellular compartments. Reprinted, with permission, from Ref. [10].

cellular debris [25]. It involves binding to specific membrane proteins. Here, the particle needs to be first coated by proteins (e.g., antibodies) to be recognized by membrane proteins.

Toxicities of carbon nanotubes

Pristine CNTs with highly hydrophobic surfaces tend to aggregate in cell culture medium, which results in binding to various biological species including protein via hydrophobic interactions leading to cellular toxicity. Several mechanisms of CNT-induced cytotoxicity have been proposed including penetration of cell membrane, oxidation of intracellular components, DNA damage, interruption of electron transfer and formation of reactive oxygen species (ROS) [36]. CNTs can disrupt the cell membrane during penetration leading to cytotoxic effects. Such disruption is related to the physicochemical properties that promote cell-membrane penetration [7] such as CNT dimensions, surface properties (functionalization) [6] and formation of corona with biomolecules [10]. Several review articles have been published to highlight the various parameters responsible for CNT-induced toxicity [8,16,30,36,37]. *In vitro* and *in vivo* experimental results of CNT toxicity studies reveal that various factors such as size, shape, composition, impurities or residual metal (cobalt, nickel, molybdenum, etc.) as well as preparation methods incorporate the toxicities in CNTs. Further, the methods of administration of CNTs (oral, inhalation, transdermal, subcutaneous, intraperitoneal and IV injection) to the human body affect the toxicity elicitations of

CNTs and must be considered judiciously [20,21]. Some studies revealed that oral, dermal and IV administration of CNTs might cause mild inflammation, whereas inhalation of CNTs can lead to severe inflammation. For example, depending upon the method of administration, the exposure of NPs (mainly pristine CNTs) to the respiratory system can lead to asthma, bronchitis or lung cancer [38,39], whereas entry through the gastrointestinal tract (GIT) might result in Crohn's disease and colon cancer. Similarly, long exposure to the systemic circulation might cause blood clotting and various heart diseases [40–43].

Mechanism of cytotoxicity by carbon nanotube exposure

Cellular damage in response to various types of CNT exposure takes place by following either of the three types of cell death programs: apoptosis, autophagy, necrosis [44]. It has been observed that CNT exposure to cells can result in lysosomal damage and consecutive release of digestive enzymes leading to apoptotic and necrotic cell death. Several experiments also revealed that CNTs could decrease mitochondrial membrane potential (MMP) leading to the formation of ROS. High levels of ROS are an indication of oxidative stress which can damage the cell by disrupting DNA, altering gene transcription, protein structure and/or cell signaling. It was evident that the treatment of rat lung cells with varying concentrations of MWCNTs (0.5–10 μg/ml) resulted in apoptosis through mitochondrial damage [45]. Although functionalization of CNTs reduces the toxicity, one of the studies showed that the COOH-linked SWCNTs induced autophagy in lung adenocarcinoma A549 cells [46].

Strategies to circumvent carbon nanotube toxicity

The functionalization of CNTs is one of the major approaches to improve the aqueous solubility and biocompatibility while reducing the toxicity, as well as aggregation, in contrast to hydrophobic pristine CNTs [16]. Although there are many ways to chemically functionalize CNTs, one of the most promising results was observed with PEG functionalization of CNTs, where PEG-CNTs were found to reduce the toxicity and reticuloendothelial system (RES) capture while improving the pharmacokinetic properties including the prolongation of blood circulation half-life [47]. A very low PEG-CNT-induced toxicity was found to be associated with very high doses of CNTs. Similarly, other studies demonstrated very low cell inflammation and mitochondrial destruction at very high doses of ammonium-functionalized CNT and Tau-linked CNT, respectively, as compared with pristine CNTs [48].

It has been observed that residual impurities of metal catalysts (Co, Fe, Ni and Mo) encapsulated in graphene layers following CNT synthesis can result in cell death through mitochondrial destruction and oxidative stress. In this regard, purification of CNTs by ultra-sonication is another important approach that can significantly reduce the cytotoxicity by promoting the release of metallic impurities into solution [49].

Effects of biophysical parameters on carbon nanotube interaction with the cell membranes

The cell membrane is mainly composed of lipids (saturated and unsaturated), cholesterol and embedded proteins [50]. The interactions between cellular, environmental and NP factors determine the CNT internalization within the cell (Fig. 5). For example, the composition of the cell membrane can affect CNT penetration. The attachment of viral glycoproteins (e.g., hemagglutinin) with cell membrane receptors is important to initiate fusion [51]. Such a technique can also be followed to design CNTs for intracellular delivery of drugs and genetic materials. The force required to rupture the cell membrane by CNTs is related to several factors of the membrane composition. For example, the presence of cholesterol (up to 30%) reduced the bending of the membrane, as a result of which the force required to puncture the membrane by CNTs is increased by 15 kcal/mol, and higher lipids were extracted during CNT penetration [9].

Molecular dynamics simulation of carbon-nanotube–cell-membrane interactions

The interaction between CNTs and biomolecules can be studied experimentally. However, molecular simulation studies offer a detailed description of the process over time [28]. MD simulation can be used to study various drug nanodelivery systems such as those based on dendrimers, polymer micelles, liposomes and CNTs [52]. The computational study of a drug-CNT–cell-membrane complex is essential for rational design of CNT-based nanodelivery systems. There are trials to reproduce the experimental adsorption of aromatic compounds on pristine and functionalized CNTs using MD simulation [53]. The MD simulations correlated with experimental results can explain the mechanism of drug delivery [54], rate of drug release [55], the observed aggregations of CNTs on cell membranes [56] and the selection of proper suspending medium for CNTs [57].

Therefore, the computer-aided simulation studies can be used to find out the optimum parameters required for designing nanodelivery systems. In this regard, MD simulations provide valuable information about the thermodynamic convergence of the system over time using classical Newtonian mechanics [13]. Classical mechanics can represent a CNT–membrane system as a set of charged atoms (balls) connected by flexible bonds (springs). However, several less important representations for atoms, interactions, as well as bond flexibilities and vibrations can be omitted to simplify the calculations. Owing to the large molecular size of the CNT–cell-membrane system, and the need to run the simulation for a long time (up to milliseconds) to achieve convergence, several approaches have been introduced to reduce the computational costs with minimal effect on precision. Such approaches include the use of constraints and restraints.

For constraint, a fixed value is given for a known variable during simulation, such as for bond length and angle size [58], which can also extend to turn a whole flexible functional group or molecule into a rigid bead; [59] or by setting a weak, long-distance interaction to zero [60]. In restraint, an energy penalty or external force is applied to the system to perturb the conformational ensembles and direct the convergence toward a specific point [61]. Specific sets of constraints and restraints are implemented in coarse-graining and steered MD, respectively. However, coarse-graining MDs obey a Newtonian or Hamiltonian equation of motions whereas steered MDs do not [62]. Therefore, the energy calculation is different in both the cases (discussed below).

Types of carbon-nanotube–membrane models used for molecular dynamics simulation

Owing to the large sizes and complexity of the systems (CNT–membrane model), several techniques are used to tackle the

problems of computational cost by using simplified MD. As discussed previously, the simplifications include the use of the simplified model (addition of constraints) which is mechanically governed by a simplified forcefield; however, such simplifications are consistent with the original model and forcefield [63]. Whether atoms are treated individually (all-atomistic), as groups (coarse-grained) or both (hybrid systems), the forcefields are available to carry the system toward convergence [64]. Accordingly, CNT interactions with biomolecules can be studied by following various MD approaches such as all-atomistic molecular dynamics (AAMD), coarse-grained molecular dynamics (CGMD), hybrid all-atomistic/coarse-grained molecular dynamics (AA/CGMD) and dissipative particle dynamics (DPD).

All-atomistic molecular dynamics

In this system, all atoms are represented explicitly including water molecules (if water is not represented implicitly). The interatomic interactions (whether bonded or nonbonded) can be represented by several forcefields of different principles such as *ab initio*, semi-empirical and empirical forcefields. The first two forcefields are computationally expensive and help to simulate bond breakage and formation during dynamics. However, the empirical forcefield is the most commonly used in MD simulation for biomolecular systems. The empirical forcefield equation includes terms for nonbonded interactions such as van der Waals, H-bonds and electrostatic, as well as terms for molecular mechanics such as bond stretching, bending, angles and dihedrals. More-complex forcefields include additional terms accounting for atomic polarizability [65]. Each term in an empirical forcefield is multiplied by a coefficient value that can be adjusted to reproduce the experimentally observed energy [66,67].

The AAMD simulations can be run with implicit or explicit water models. Most of the AAMD simulations with explicit water models use nonpolarizable and orientation-independent water models that have lower computational costs such as TIP3P, SPC/E and TIP4P, respectively [68]. The TIP4P is an improved water model [69]; however, it shows anomalous movement inside the CNT which is not perceived with the TIP3P model [70,71]. Also, water viscosity within CNTs seems to increase in direct relation to temperature and size of CNTs during MD simulation [72]. These observations necessitate the precise choice of water model during CNT simulation. Although the implicit water model adds approximations on the calculations, the reduction in computational cost is not guaranteed [73].

Among the most commonly used empirical forcefields are CHARMM [74,75], AMBER [76,77], united-atom GROMOS [78] and COMPASS [79]. These forcefields have been used to model the systems of molecular interactions between CNTs and proteins [15,80–82], nucleic acids [83–85] and drug molecules [23,86–90]. Despite being computationally expensive, AAMD can also be used effectively for studying CNT interactions with the cell membrane [9,14].

Coarse-grained molecular dynamics

CGMD methodology is used to simulate the mechanics of mesoscopic systems (< 1 μm) depending on the statistical coarse-graining description [91]. This technique depends on reducing the number of degrees of freedom as compared with the AA description, thus eliminating the fine interaction details. In this approach, the atoms are united together by merging nonpolar hydrogens bound to carbon, the addition of constraints to remove the highest frequency motion from the system or simplifying a group of atoms into a single bead. Some types of coarse-grained models add restraint to preserve the conformation for a macromolecule (e.g., protein domain) during MD simulation [92].

The coarse-grained model for cell membrane phospholipids can include three types of particles: tail particle to represent four methylene groups [-$(CH_2)_4$-], water particle to represent four water molecules and a head particle to represent the part of the head of the phospholipid, as shown in Fig. 6 for the DPPC lipid [93]. CGMD is usually used for large molecular systems where the interaction types are limited but repeated like the system of CNTs with cell membranes [94–97], polymers [98], solvent/detergent/lipids [99,100]. Owing to the low computational cost of CGMD as compared with AAMD, the simulation period can be extended up to microseconds. Moreover, CGMD can also be used in simulating CNT interactions with proteins [101], carbohydrates [102], DNA [103,104] and with other NPs [105]. Several types of phospholipids with their atomistic and coarse-grained representations as well as chemical names are provided in Fig. 6 [106].

There are several types of forcefields used in CGMD. The coarse-grained forcefield commonly used for CNT–membrane systems such as the MARTINI forcefield is a parameterized form of AA forcefield. This forcefield follows top-down approaches (i.e., a parameterizing classical AA forcefield) to reproduce some experimental observations using coarse-particle representation for the system. The MARTINI forcefield uses Lennard–Jones interactions but with adjusted well depth (ε) to reproduce observed partition coefficients. The electrostatic interactions are also included in this forcefield as simple Coulombic potentials, whereas harmonic potentials define the length and angle for the bonded interactions [27,107]. Although the MARTINI forcefield works well for several systems, it is not efficient in describing some interactions such as water behavior at the water–solid interface where abnormal freezing can take place [108]. However, this unwanted freezing can be minimized by using special large particles known as antifreezing particles [109]. Like AAMD, implicit water models are currently used with the coarse-grained forcefield such as the new Dry MARTINI forcefield which was reported to produce significantly quicker calculations [110].

Hybrid all-atomistic and coarse-grained molecular dynamics

In this methodology, some regions of the system are modeled as AA and others as coarse-grained [111] like mixed quantum mechanics/molecular mechanics dynamic simulations. The AA/CG hybrid system requires the description of the interaction at the interface such as those of electrostatic and van der Waals interactions. The forcefield required to represent the AA/CG hybrid system is derived from the forcefield representing the AA system (AA–AA), which is then mapped on to CG–CG interactions. At the interface, the AA molecules are mapped to coarse-grained particles, and the center of the mass is recalculated. Thus, a simple CG–CG interaction is being computed. The force generated from the interaction is then distributed on the atoms comprising the particle using mass-weighting [112]. Such a technique is preferred in cases where full atomic details are required at the interaction site such as for CNT–membrane [113] or more importantly for protein–membrane systems [111]. Some experiments use AA and

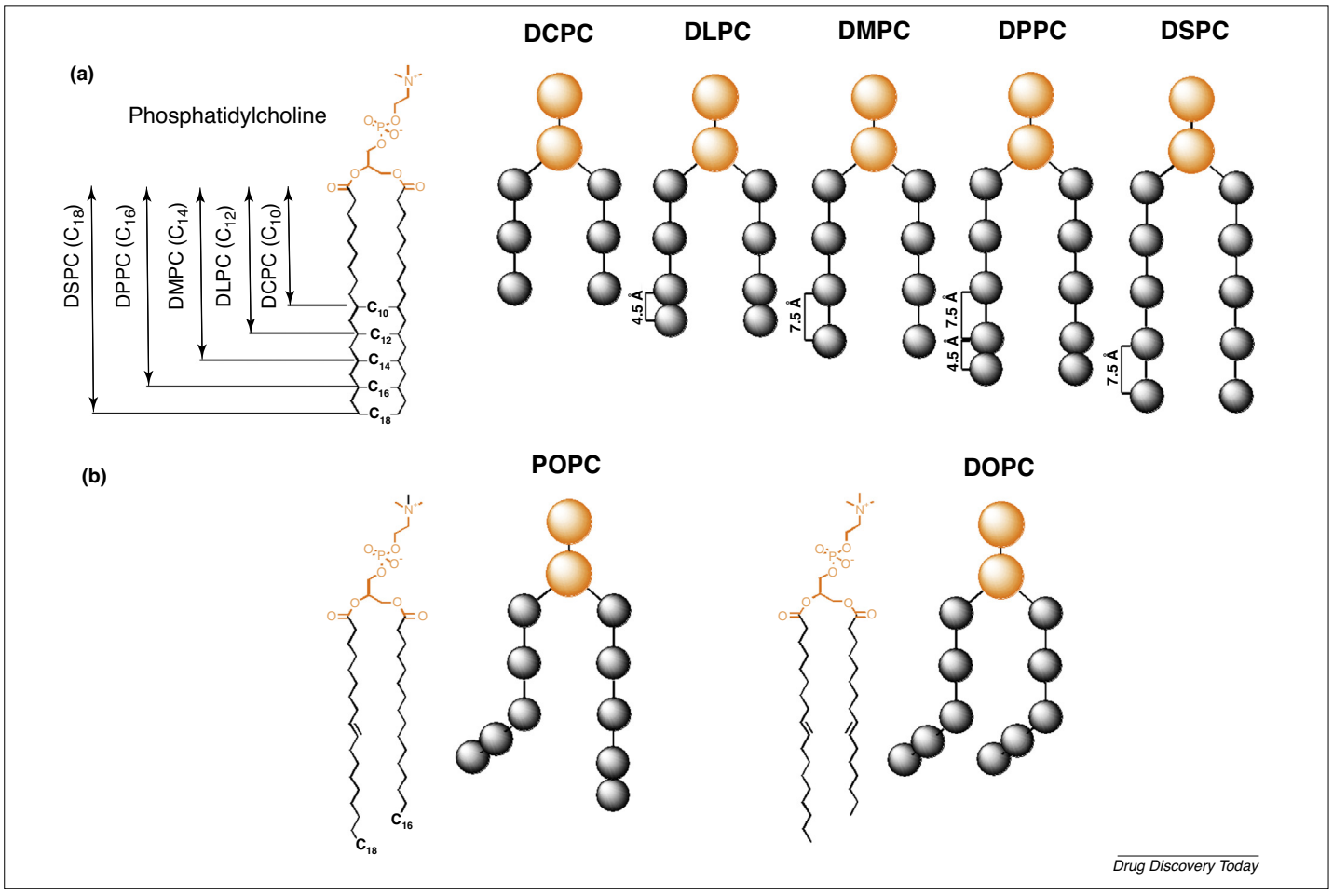

FIGURE 6

Molecular representations for phospholipids using all-atomistic and coarse-grained models for **(a)** saturated phospholipids such as 1,2-dicaproyl- *sn*-glycero-3-phosphocholine (DCPC), 1,2-dilauroyl-sn-glycero-3-phosphocholine (DLPC), 1,2-dimyristoyl-*sn*-glycero-3-phosphocholine (DMPC), 1,2-dipalmitoyl-*sn*-glycero-3-phosphocholine (DPPC) and 1,2-distearoyl-*sn*-glycero-3-phosphocholine (DSPC); as well as **(b)** unsaturated phospholipids such as 1-palmitoyl-2-oleoyl-*sn*-glycero-3-phosphocholine (POPC) and 1,2-dioleoyl-*sn*-glycero-3-phosphocholine (DOPC). Orange beads correspond to hydrophilic groups and gray beads correspond to hydrophobic groups [106].

coarse-grained models but as a non-hybrid system where the model is switched between AA and coarse-grained models during MD simulation. After convergence using CGMD, the AA details can be restored, and the simulation can be continued with AAMD. Various algorithms are available to map AA to coarse-graining and vice versa [114,115].

Dissipative particle dynamics

This the simplest and computationally cheapest type of simulation in which a single particle represents a group of molecules. It can be used for colloidal systems where particles undergo Brownian motion within the solvent. The approach is similar to MD, where the forces acting on the particles are divided into conservative force (i.e., pair-wise potentials), dissipative force (i.e., due to friction) and random force [116]. The frictional as well as random forces in Brownian dynamics do not conserve momentum. However, in DPD the frictional and random forces obey action-equals-reaction as a result of which the model conserves momentum [117]. The implicit solvent modeling in DPD was also reported to increase the speed of calculations [118]. The DPD technique is more grained than the coarse-grained model and frequently used to simulate hydrodynamic behavior for CNTs with other materials such polymer mixtures [119–121], surfactants [122,123] and water [124,125], as well as studying the macroscopic physical behavior of CNTs [126].

Free energy calculations from molecular dynamics simulation studies

MD simulation can be performed under constant pressure, temperature and number of particles to achieve the thermodynamic equilibrium. However, achieving equilibrium for large complex systems (such as CNTs and cell membrane) is computationally costly [127]. Therefore, for extremely large systems, the simulation is usually accelerated toward convergence by applying an external force to cross the energy minima. However, this leads to non-equilibrium simulation known as steered MD simulation.

The free energy for systems based on equilibrium or quasi-static simulation can be calculated using thermodynamic integration [128] and umbrella sampling [129]. Regarding non-equilibrium simulation the affinity of ligand interaction to the receptor can be

estimated from the energy essential to pull the ligand out of the receptor, which is an analog for atomic force microscopy [130]. Thus, rather than binding free energy, the rupture force is measured as the maximum on the force-time/displacement profile and used as a scoring function known as the potential of mean force (PMF) [131]. The PMF can be determined using Jarzynki's equation (Eq. (3)) under constant temperature and pressure [132,133].

$$e^{-\beta\Delta G} = e^{-\beta W} \quad (3)$$

where $\beta = 1/k_B T$, the k_B is the Boltzmann constant, T is the temperature, G is Gibbs free energy and W is the work done. The integration of force along the direction of steering gives the free energy.

For example, the PMF required for CNTs to penetrate the cell membrane is about tens of pN before the start of membrane curvature. Membrane curvature is a defect observed in the membrane due to the exposure of hydrophobic tails of lipids to water that results in the elevation of PMF to thousands of pN. However, PMF reduces when hydrophobic tails start wrapping around CNTs [9].

Molecular dynamics simulation studies of cell membrane internalization of carbon nanotubes

Many observations in physics, chemistry, biology and other material sciences can be simulated using MD simulation. The accuracy of simulation results depends on the proper molecular representations of ligand, receptor and medium, as well as a selection of valid forcefield and sufficient sampling [134]. The cell membrane is composed of different lipid molecules such as phospholipids, cholesterol and glycolipids. However, only a single type of phospholipid is represented during MD simulation [135]. The MD simulations usually follow the framework of the isobaric–isothermal ensemble (NPT), which is known as a favorable ensemble for membrane simulations [14,27,95]. As the size of the system increases, a longer simulation time is required to achieve convergence (up to microseconds). Therefore, to extend the simulation time for the system, the number of atoms, degrees of freedom and interactions of short range need to be reduced by grouping atoms into particles (coarse-grained) that interact with each other by a modified forcefield over long integration time steps (CGMD simulation). Such CGMD simulation can be used to simulate huge systems up to the size of fully enveloped influenza-A virus in the microsecond time-scale [136]. The loss of accuracy owing to the coarseness can be reduced if atomistic detailing is applied at important interaction sites as in AA/CGMD simulation [137].

Usually, simulation of CNT–membrane interactions requires the use of CGMD [138]. Using a single snapshot of an AA model, the coarse-grained model is generated which usually involves 4:1 atom-mapping of the carbon atoms in order to preserve the hexagonal symmetry of the CNT lattice [139]. Recently, coarse-grained models compatible with the popular coarse-grained MARTINI forcefield [109] can be automatically generated based on atomistic simulation trajectories, rather than fitting to a single snapshot, thus providing more-accurate representation for the model [140]. In their review article, Ingolfsson *et al.* discussed in detail the various developed coarse-grained forcefields [141]. The MARTINI coarse-grained forcefield was initially developed for lipids; however, the use of this forcefield was further extended and explored for proteins [101,142], carbohydrates [102], DNA [103], polymers [98] and other NPs [105]. The experiments commonly conducted for CNT interactions with cell membranes are either thermodynamically equilibrated (i.e., penetration is driven by forcefield interactions only) or non-thermodynamically equilibrated (i.e., injection mainly driven by an external force).

Cell membrane penetration

In this method, the MD simulations are usually carried out by manually placing CNTs at a reasonable distance from the interacting molecules like membrane [143] or protein [144], among others. For nonfunctionalized CNTs, van der Waals and hydrophobic interactions are the dominant interactions to be simulated [145] usually with explicit water representation [97,143].

The MD simulation can provide insight into the effect of length and chirality of CNTs on cell membrane penetration [95,143]. If MD is allowed to run without constraints, the CNTs (~6 nm in length) can tilt during membrane embedding until the tube is completely buried within the hydrophobic part of the bilayer [143]. Interestingly, the chirality of CNTs affects the rate of membrane penetration. For short CNTs (less than one membrane thickness), the rotation (tilt) during penetration is obvious, and the effect of chirality on penetration is minimal. However, if the length of CNTs equals twice the membrane thickness, the effect of chirality becomes pronounced and the penetration of the membrane gets faster with lower chiral indices (higher aspect ratio) owing to lower adhesion to the membrane [146]. Accordingly, the MD simulation can be used to adjust the physical properties for CNTs for customized drug delivery.

MD simulation can complement the transmission electron microscope to describe the mechanism of cell membrane internalization for amino-functionalized CNTs. The hydrophilic and positively charged functional groups of the surface guide the CNT orientation to be parallel concerning the membrane axis to maximize the interaction with the negatively charged membrane. Subsequently, the CNTs adopt a perpendicular orientation during internalization as mediated by CNT hydrophobicity [147]. The degree of functionalization affects the penetration angle [148]. The length of the CNTs is another important factor, CNTs <1 μm in length have a higher ability to penetrate the cell membrane than longer ones [129]. Simulations and experiments showed incomplete uptake of long CNTs by lysosomes which could eventually lead to activation of apoptotic signals and cell death [94]. Moreover, different mechanisms of internalization are observed for capped and non-capped CNTs [149].

MD simulation can provide optimum conditions for drug loading into CNTs and unloading at the cell membrane. Larger diameter CNTs are favored as drug carriers and the π–π interaction is the main interaction between the CNT aromatic rings and lone-pair electrons of the drug such as those of oxygen atoms [150]. MD can simulate the effect of other parameters on drug loading such as temperature, solution composition [151], as well as the unloading parameters like water effect and interaction with the cell membrane [90]. For example, the loading of vinblastine on CNTs was favored with terminal esterification of CNTs with armchair chirality [152]. For cisplatin, the insertion within CNTs and release at the cell membrane was dependent on water dynamics [90]. CNTs can also function as mediators for liposomal package fusion with the cell membrane by reducing the energy barrier [153]. The effect of covalent and noncovalent functionalization of CNTs by PEG on

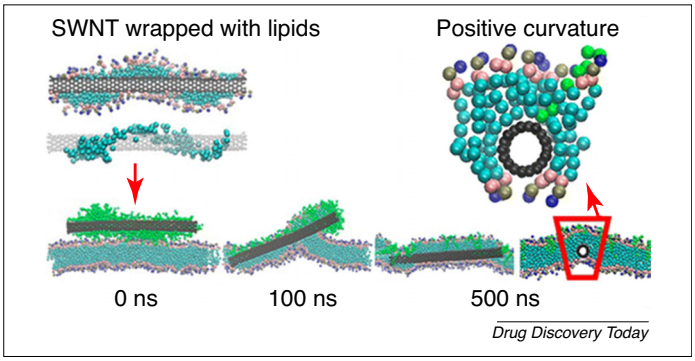

FIGURE 7

Snapshots from molecular dynamics (MD) simulations for membrane penetration of carbon nanotubes (CNTs) wrapped with different types of lipids and polyethylene glycol (PEG)-grafted lipids were simulated with lipid bilayers over 500 ns of MD. Reprinted, with permission, from Ref. [154].

cell membrane penetration and the aggregation of CNTs was studied using MD simulation (Fig. 7) [154]. The results showed that covalent functionalization with PEG enhanced dispersion but not membrane penetration, whereas the opposite was observed for noncovalent functionalization [155]. The enhancement of membrane penetration by proper selection of type and density of noncovalent functionalization can also be simulated [156].

Cell membrane injection

This type of simulation study can help to determine the structural properties in CNTs that are required for proper penetration with minimal damage to the cell membrane as well as for delivering the attached drug molecule at the site of penetration. The penetration of CNTs through the membrane can be enforced by using steered MD where external force and restrain are applied. For example, a spring connects CNTs to a dummy point moving with constant velocity across the membrane using a constant of 5–10 kJ mol^{-1} $Å^{-2}$ and the orientation of CNTs can be restrained with 10 kJ mol^{-1} $Å^{-2}$ during the movement [14,96]. The speed of the dummy atom can be 0.025–0.1 Å/ps which gives a force of pulling CNTs through the lipid membrane ranging from 1400 pN at the insertion or leaving stages to 400 pN when the tube is midway within the membrane. During the insertion, the hydrophobic CNT surface is resisted by the hydrophilic phase of the membrane, in addition lipid molecules move upward to wrap the CNT surface exposed to the aqueous medium. During the leaving phase, the hydrophobic CNT surface is detached from the hydrophobic core of the membrane and some lipid molecules are extracted from the membrane. Therefore, different forces are measured according to CNT displacement concerning the cell membrane (Fig. 8).

The force acting on the dummy atom (PMF) can be calculated from the potential energy using Eqs (4) and (5):

$$F = -\nabla U \tag{4}$$

$$U = \frac{1}{2}k[vt - (r - r_0).n]^2 \tag{5}$$

where ∇U is the potential energy gradient, k is the spring force constant, v is the velocity of pulling, t is the current time, r and r_0 are the instantaneous and initial positions, respectively, and n is the vector direction of the dummy atom [9,14].

Although steered MD does not represent the real thermodynamic behavior of the system, it can be used to simulate the behavior of frequently employed nano-injectors [157,158]. It has been observed that a higher speed of penetration (up to 50 Å/ns) can provide lower membrane perturbation in the direction antiparallel to the pulling force as well as less CNT blockage during insertion into the lipid membrane, especially for small-diameter CNTs (<25 Å). The force required to inject CNTs (14–50 Å diameter, 50–100 Å in length) was computed to be almost 600 pN [96]. The MD simulations can provide information about stress points on CNTs, optimum chirality (tilt angle) and the speed that promotes penetration with minor destructive or deflective effects on the cell membrane and CNTs [159]. Examples of recently conducted experiments for CNT–membrane interactions using different types of models, forcefields and lipids (with or without steering) are provided in Table 1. Although several commercial and noncommercial software packages are available to handle MD simulation for CNT systems, GROMACS is regarded as the most

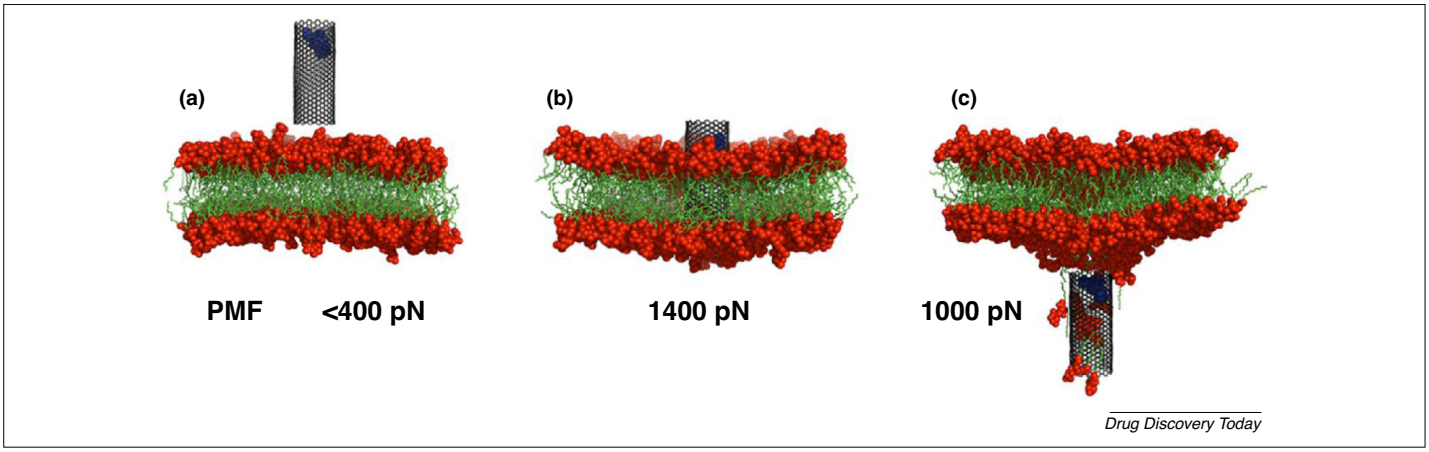

FIGURE 8

Snapshots of carbon nanotube (CNT)–paclitaxel membrane injection using steered molecular dynamics (MD). The calculated potential mean force (PMF) for penetration varied according to displacement of CNTs concerning the membrane. Reprinted, with permission, from Ref. [14].

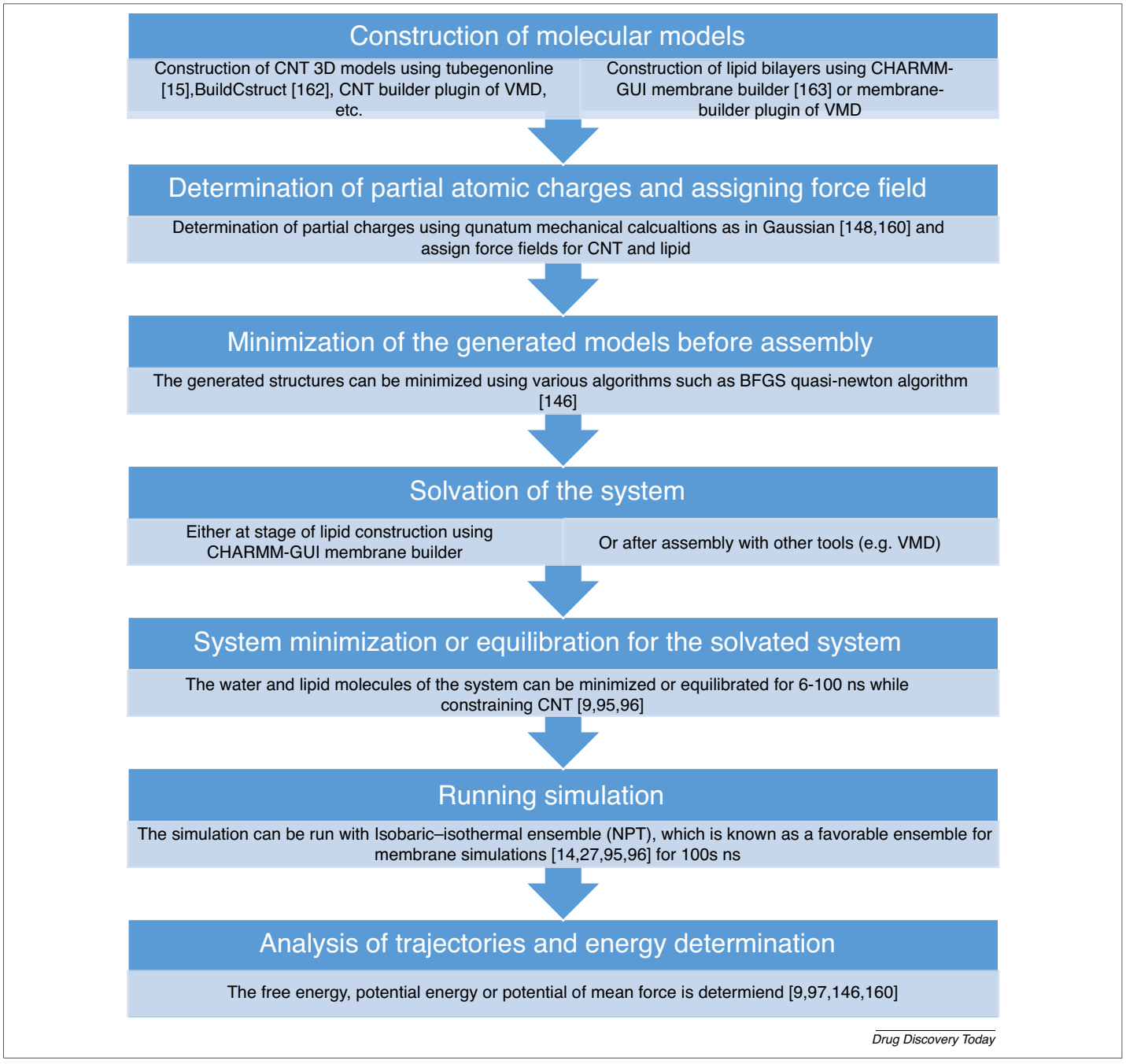

FIGURE 9

Workflow to set a CNT–membrane MD experiment [162,163].

commonly used because it implements AA forcefields (AMBER, CHARMM, GROMOS and OPLS) as well as coarse-grained forcefields (MARTINI). A workflow for a CNT–membrane MD experiment is shown in Fig. 9.

Limitations of carbon-nanotube–membrane molecular dynamics simulations

Limitations of the MD approach in general include lower precision in forcefields to represent experimental observations, size-limits for the system being simulated and computational demands. CGMDs on their own, however, have limitations of being not transferable (i.e., not able to efficiently address atomistic model), the forcefields are only parameterized for specific classes of molecules and they are too coarse to capture certain behavior such as H-bond directionality [142]. Improvements in forcefields and multiscale automatic transferability between AA and coarse-grained modeling are recommended to reduce the CGMD inaccuracy and to enable experimental data reproducibility. Improvements in algorithms and computational speed are required to achieve system convergence easily. With previous improvements, the MD

TABLE 1

Molecular dynamics experiments for carbon-nanotube–membrane interactions

MD type	MD software	MD forcefield[a]	MD steering	Lipid	CNT placement	Refs
AAMD	NAMD	CHARMM	Yes	POPC	Manual; 1 nm above membrane	[9]
AAMD	NAMD	CHARMM36	Yes, only CNT orientation is constrained	DOPC	Manual	[160]
AAMD	TINKER	CHARMM27 + MM3	NO	DPPC	Manual above membrane by 2 Å	[146]
AAMD	GROMACS	GROMOS43A1	Yes	DPPC	Manual; 1 nm above membrane	[14]
AAMD	AMBER	AMBER	NO	DOPC	Manual above membrane	[143]
CGMD	GROMACS	MARTINI	NO	DPPC	Manual above membrane	[95]
CGMD	GROMACS	MARTINI	NO	DOPC	Manual above membrane	[97]
CGMD	GROMACS	MARTINI-like	Yes, only CNT orientation is constrained	DPPC	Manual	[27]
CGMD	GROMACS	MARTINI	Yes	DPPC	Manual above membrane by ~30 Å	[96]
GCMD	GROMACS	MARTINI	Yes	DPPC, DHPC,[b] LPC	Manual; 3 nm above membrane	[99]
AA/CG MD	OCCAM	Specific[a]	NO	DPPC	Manual above membrane	[113]
DPD	Unknown	Specific[a]	YES	General	Manual; 1.6 nm above membrane	[161]

[a] MD forcefield is designed by the researchers.
[b] DHPC = 1,2-diheptanoyl-*sn*-glycero-3-phosphocholine.

simulation is expected to be a standard step in rational design of CNT-based nanodelivery systems.

Concluding remarks

The CNT-based target-specific delivery of drugs, or other molecular cargo, has emerged as one of the most potential biomedical applications of nanotechnology. To achieve efficient CNT-based nanodrug delivery, the interactions between the drug, CNT and biomolecular target need to be properly optimized. Further, inappropriate physicochemical properties of CNTs can disrupt the nuclear or cellular membrane during penetration leading to various cytotoxic effects. The CNT–bimolecular interactions can be optimized by adjusting the various physicochemical properties of drugs and fine-tuning the several parameters of CNTs to achieve effective drug delivery while avoiding toxicities. Recent advances in the computer-aided molecular design tools, in particular MD simulation studies, offer an appropriate low-cost approach for such optimization. This review highlights the various potential MD simulation approaches along with their strengths and weaknesses in current use for the simulation of CNT interactions with the cell membrane. An attempt has also been made to emphasize the various methods of internalization and toxicities of CNTs. The detailed analysis of several MD approaches discussed in this review will be useful to build new strategies to develop the necessary computational setup for designing rational CNT-based targeted drug delivery to circumvent the limitations associated with the clinically available various nonspecific therapeutic agents.

Conflicts of interest

The authors confirm that there are no conflicts of interest associated with this article.

Acknowledgments

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