Role of Computational Modeling in the Design and Development of Nanotechnology-based Drug Delivery Systems

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Nanoparticle formulation development for drug delivery, a crucial aspect of nanotechnology, encounters numerous challenges. These encompass selecting appropriate excipients, comprehending miscibility and solubility factors, ensuring efficient drug encapsulation and release, assessing stability, and facilitating drug transport in the bloodstream for accurate targeting and attachment. To address these intricate issues, a range of molecular computational models is utilized. These models include quantum mechanical simulations that handle the smallest particles and move through atomistic molecular dynamics for detailed molecular interactions, coarse-grained molecular dynamics (MD) for larger scale phenomena, and dissipative particle dynamics (DPD) for mesoscale modeling. Further scaling up, computational fluid dynamics (CFD) is used for fluidic behaviors, discrete element modeling for large particle systems, and both pharmacokinetic/pharmacodynamic (PK/PD) and physiologically based pharmacokinetic (PBPK) modeling for whole-body dynamics. These methodologies play a crucial role in elucidating the complex mechanisms involved in the development of nanoparticle formulations and are essential in the creation of varied organic and inorganic systems for drug delivery. This review primarily concentrates on these computational simulation models and their significance in the context of nanoparticle-based drug delivery systems.

Keywords
nanoparticles, drug delivery, computational modelling, drug release dynamics, simulations

Introduction

The pathway of drug discovery and development plays an essential role in identifying active compounds for treating and preventing diseases. This conventional process is time-consuming and costly. The different stages of this process are depicted in Fig. 1.

In recent times, computational simulations have emerged as a crucial tool in addressing the limitations associated with traditional methods of drug development. They offer a near-accurate model that expedites the drug development cycle, and are extensively applied in various phases of drug discovery. The initial phases involve the identification and characterization of potential therapeutic targets, understanding their function and role in disease pathology. Subsequently, the molecular interactions of these targets are explored. Techniques such as pharmacophore mapping and inverse docking are instrumental in filtering out a broad range of

targets to a more focused group of active candidates. A promising target must fulfill criteria of efficacy, safety, and meet both clinical and commercial benchmarks, playing a pivotal role in disease mechanism and its therapeutic modulation. Sophisticated computational strategies like molecular docking, pharmacophore modeling, de novo design, virtual library creation, quantitative structure–activity relationships, and sequence-based approaches are utilized for refining and confirming these targets.

Further, computational simulations are integral in later stages of drug discovery, including preclinical trials. Nanotechnology-based systems encompass a diverse range of formulations including liposomes, polymeric nanoparticles, dendrimers, and metallic nanoparticles, each suited to specific therapeutic targets due to their unique properties. These systems promise efficient and targeted delivery mechanisms for treating severe diseases but involve complex design challenges. Liposomes are spherical vesicles composed of lipid bilayers. Computational techniques such as molecular dynamics simulations are pivotal for studying the stability and

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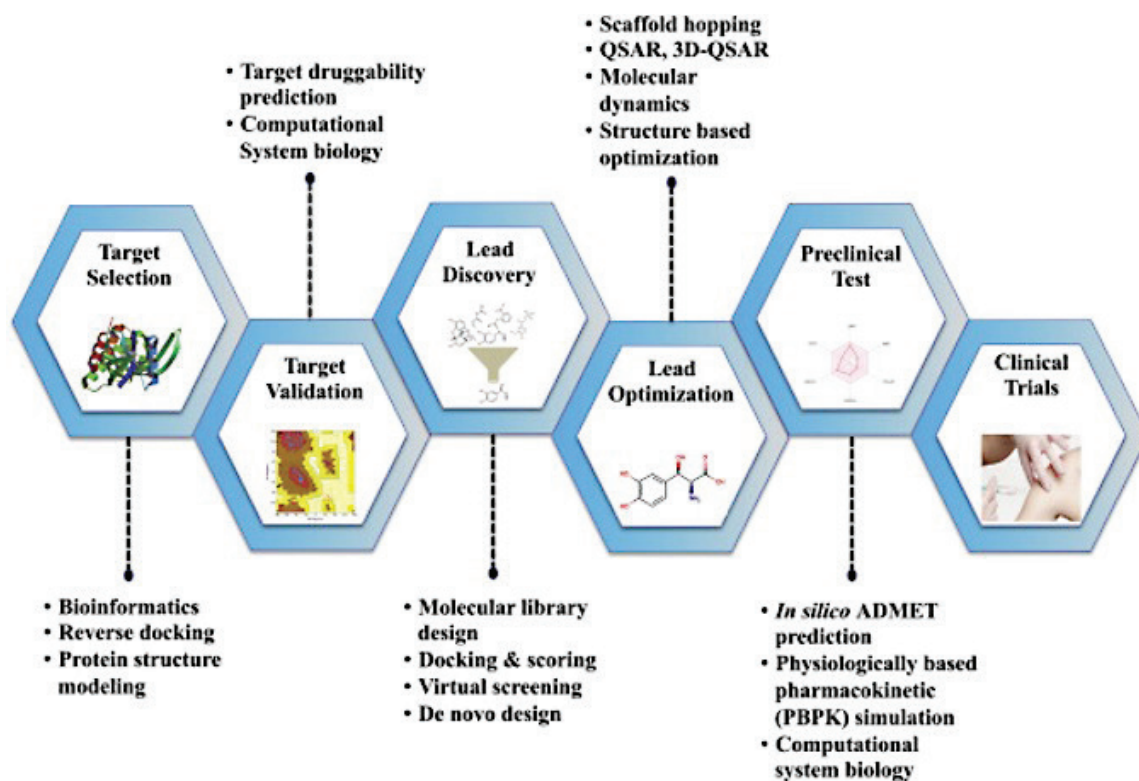e-mail: elsevarmikayilov@gmail.com

F i g. 1 – *Computer-aided drug design phases*

permeability of these bilayers, crucial for encapsulating and releasing drugs effectively. Polymeric nanoparticles involve the use of biodegradable polymers for drug encapsulation. Techniques such as coarse-grained modeling and quantum mechanical simulations aid in understanding polymer-drug interactions and predicting the stability and release profiles of these systems. Dendrimers are highly branched, star-shaped macromolecules. Atomistic molecular dynamics and Monte Carlo simulations are used to explore the encapsulation capabilities and to model the interactions of dendrimers with targeted cells and tissues. Metallic nanoparticles, such as gold and silver, are utilized for their unique optical properties which can be tuned for both therapeutic and diagnostic purposes. Discrete element modeling and quantum mechanical simulations can predict the optical properties and interaction dynamics with biological molecules. Nonetheless, the development of nanoformulations is complex and arduous, encompassing numerous process parameters, expensive experimental procedures, and toxicity risks. Computational simulation acts as a preliminary screening mechanism prior to experimental trials, streamlining the process and reducing experimental demands. The combination of nanotherapeutics and computational simulation offers a molecular-level insight into critical aspects such as drug and carrier selection, drug loading, nanoformulation's interaction with biological entities, and the

rates of cellular uptake and release, aspects that would be challenging to investigate through experimental means alone.

While there has been a plethora of reviews in the past decade focusing on the application of specific computational tools in the development of nanoparticles, most of these reviews have emphasized the use of particular modeling tools in investigating crucial factors in the design of various nanoplatforms, as indicated in references[3,4]. However, a significant gap exists in the literature concerning the application of a comprehensive range of modeling approaches across different nanoplatforms[5].

Particular studies have primarily concentrated on multiscale modeling to examine factors affecting interactions between nanoparticles and cell membranes[6,7], as well as their behavior in complex blood networks[11]. For an in-depth theoretical understanding of these computational methods, the detailed works of Yu *et al.* and Casalini[1,2] are recommended.

There are no reviews that thoroughly discuss the latest advancements in simulation tools across every pivotal phase of nanoparticle development. The intricate process of targeted and efficient drug delivery continues to be a critical subject in ongoing research. This review delves into the recent developments in computational simulation, offering an understanding of the atomistic-level interactions in nanoparticle formulation design. This review also underscores the significance and utility of computer

simulations, ranging from the initial screening of process variables to the ultimate evaluation of therapeutic efficacy.

Role of computational tools in the development of nanoparticle formulations

In the realm of nanoparticles formulation, computational simulation tools play a crucial role in advancing our comprehension and forecasting the self-assembly characteristics of drugs, their molecular interactions, and biological functionalities. These tools are pivotal for screening a vast array of excipients, determining the most effective drug-excipient combinations, and forecasting aspects such as solubility, self-assembly, formation of nanoparticles, drug encapsulation/loading, drug release, stability considerations, interactions with cell membranes, cellular absorption processes, and the overall therapeutic efficacy in biological systems. Quantum mechanical methods apply the principles of quantum mechanics to predict molecular structures and interactions, focusing on binding energies, dipole moments, and atomic interaction details that are crucial for understanding nanoparticle behavior at the most fundamental level. It provides detailed electronic structure analysis and it is precise for small molecular systems. However, quantum mechanical meth-

ods are extremely computationally demanding and not feasible for large systems or long durations. Full atom molecular dynamics offers a detailed simulation of all atomic movements, providing insights into binding activities at the molecular level on polymer surfaces, and the impact of such interactions on physiological processes like blood flow. Full atom molecular dynamics provides high detail at the atomic level and accurate modeling of physical and chemical properties. However, it is computationally intensive and limited to smaller systems and shorter time scales. Coarse-grained modeling simplifies complex molecular systems by reducing the degrees of freedom represented in simulations, utilizing methods like dissipative particle dynamics and coarse-grained molecular dynamics to manage macroscopic interaction simulations including repulsive and electrostatic forces. Coarse-grained modeling balances detail and computational efficiency, making it suitable for moderately large systems. However, it loses atomic-level detail, and its accuracy depends on the quality of parameterization. Continuum modeling employs continuum mechanics principles, treating materials as continuous distributions, and integrates mechanistic pharmacokinetic/pharmacodynamic (PK/PD) and physiologically based pharmacokinetic (PBPK) models. This technique provides insight into the distribution and elimination of nanoparticles in biological systems. The advantages of continuum modeling include its

T a b l e 1 – *Computational tools used in nanocarrier-based formulation design*

No.	Simulation techniques	Summary	Application	Citations
1	Continuum Modeling	Mechanistic PK/PD and PBPK modeling techniques offer a deep dive into the impacts of nanoparticles physical and chemical properties on their distribution and elimination patterns in biological systems.	They are utilized for forecasting the in vivo absorption, distribution, metabolism, and excretion of nanoparticles. Predictive modeling of drug interactions, drug release in vivo, and factors influencing nanoparticle phagocytosis and toxicity are also facilitated.	21–25
2	Coarse-grained Modeling Techniques	Utilizes techniques like Dissipative Particle Dynamics and Coarse-grained Molecular Dynamics to simulate complex interactions at a macroscopic level, including the repulsive forces between particles and the long-range electrostatic interactions.	Applications include studying the surface interaction of nanoparticles with cellular membranes, cellular uptake, self-assembly of polymers, and their drug loading and releasing capabilities.	9–14
3	Full Atom Molecular Dynamics	These molecular dynamics simulations delve into binding activities at the molecular level on polymer surfaces and analyze the impact of vasculature resistance on the rate of blood flow.	They predict drug loading capacities, solubility parameters, miscibility traits, and assess how nanoparticles distribute within blood flow.	16–20
4	Quantum Mechanical Methods	Quantum mechanics is employed to identify structures, binding energies, dipole moments, and atomic interactions, as well as solvation energies and the partitioning behavior of molecules.	Useful in structural predictions, interactions between proteins and ligands, and understanding material behaviors that influence studies on compatibility, loading, and release of drugs.	13,14

efficiency for large systems and long time scales, as well as its suitability for system-level simulations. However, its weaknesses lie in the lack of detailed molecular interactions and the potential failure to capture all microscale phenomena[9–25]. Table 1 presents a detailed application of these simulation tools.

Strategies in excipient selection and drug-excipient compatibility

Addressing challenges such as formulation instability, insufficient drug loading, and suboptimal drug retention is pivotal in the development of nanoformulations. A key area of focus is the selection of excipients and ensuring their compatibility with drugs. To circumvent the need for extensive empirical experimentation in choosing suitable excipients for drug encapsulation, computational simulations have become increasingly prevalent. This technique hastens the process of selecting excipients, effectively identifying the most conducive ones for enhancing drug encapsulation. Techniques like dissipative particle dynamics (DPD) and coarse-grained molecular dynamics (CG MD) using the MARTINI force field are utilized to investigate interactions between drugs and excipients. DPD simulations, which represent excipient molecules as distinct entities, are instrumental in forecasting interactions between drugs and polymers, and the efficiency of polymers in encapsulating hydrophobic drugs such as prednisolone and paracetamol. However, these simulations show limitations in accurately modeling interactions with hydrophilic drugs like isoniazid, highlighting a gap in simulating hydrophilic drug-polymer interactions. CG MD is effective in simulating polymer self-assembly in micelles and the distribution of drugs within these micelles[12,26].

Studies on the interaction of various drugs (such as Curcumin, Paclitaxel, Vitamin D3) with specific polymers have been conducted using molecular dynamics simulation and docking calculations. This dual computational approach also computes the binding energy between the drug and polymer, offering insights into the structural properties and interactions crucial for drug loading[16].

Another research investigated the interactions of doxorubicin with different hyaluronic acid copolymers (HA-g-glyceryl monostearate, monolaurate, and monocaprylate) through molecular modeling and Flory-Huggins interaction parameters. Among these, HA-g-glyceryl monostearate demonstrated the highest compatibility with doxorubicin, with the experimental findings corroborating the model predictions[27]. In designing effective polymeric carriers, both thermodynamic and molecular simulation methods are utilized to estimate drug-polymer compatibility using Flory-Huggins interaction parameters. These computational approaches proficiently screen various drugs against a range of polymers, aiding in the design of optimized polymeric micelles with improved drug solubility[17,27].

Prediction of drug solubility/miscibility

The miscibility of active pharmaceutical ingredients (APIs) within polymeric carriers is essential for effective drug loading in nanoparticles. Computational modeling, renowned for its proficiency in solubility prediction[28], plays a vital role in the formulation and development domain, particularly for in silico assessments of solubility/miscibility parameters and specific interactions. Cohesive energy density, a critical factor in these assessments, can be determined using various force fields depending on the molecular system under study. While the COMPASS force field has been commonly employed due to its comprehensive parameterization for a wide range of molecules, other force fields like AMBER, CHARMM, or OPLS may be more suitable depending on the specific properties and behaviors of the APIs and excipients involved. These force fields provide valuable insights into aspects such as solubility/miscibility, melting points, drug-carrier interactions, and solubility parameters derived through molecular dynamics simulations. Such simulations are instrumental in the rational selection of leading excipients for formulation development[17,18].

Advanced atomistic simulations, employing the Hildebrand solubility parameter and integrating methods like the Group Contribution Method (GCM) and molecular dynamics (MD) simulation, are critical in selecting leading excipients and evaluating drug-excipient miscibility for stable and effective drug-laden nanocarriers[19,29]. The higher the compatibility between an API and a polymer, the more soluble the API is in the nanocarrier's core, which leads to a formulation that is both more stable and has higher drug loading capacity. GCM and MD simulations were utilized to design a copolymeric micellar system encompassing 10-hydroxycamptothecin, chitosan, and three chitosan copolymers. The Flory-Huggins and Hansen partial solubility parameters, calculated through GCM and MD, revealed that chitosan copolymers exhibited greater miscibility due to their hydrophobic modification compared to chitosan[29].

Determining the appropriate solvent and anti-solvent combinations for a fixed-dose combination nanosuspension of low soluble anti-HIV drugs darunavir and ritonavir posed a significant challenge. The Hildebrand solubility parameter, calculated using MD simulation, was instrumental in

guiding the selection of solvents and anti-solvents. Subsequent MD simulations on these anti-HIV drugs facilitated the observation of phase separation and nanoparticle formation, showcasing the effectiveness of molecular simulation in reducing experimental efforts and aiding in the optimal selection of solvents/excipients for nanoparticle development[30].

Estimation of drug loading capacity

In the domain of computational-assisted drug formulation, understanding the 'cause–effect' relationships is crucial and aligns effectively with empirical results. The use of artificial neural networks (ANN) for optimizing variables like polymer concentration, coacervation agent solution concentration, stirring rate, and spraying rate has proven effective. For instance, ANN was utilized to optimize process parameters for benzimidazole chitosan microparticles, resulting in improved drug loading efficiency[31]. A combined approach employing ANN, response surface methodology, and continuous genetic algorithms was applied to investigate the ratio of drug to lipid, surfactant concentrations, and the drug loading capacity of polymer lipid hybrid nanoparticles[32,33].

Research focusing on the impact of surface functionalization (such as amine, cyano, methyl, carboxyl) on 5-fluorouracil loading in mesoporous silica nanoparticles utilized MD simulations to study adsorption behaviors and energies. The nanoparticles functionalized with amine showed higher hydrogen bond interactions and adsorption energy, consistent with experimental findings on loading capacity[34]. Docking studies with antibacterial drugs on amorphous chitin nanoparticles revealed a correlation between higher binding affinity/energy and increased encapsulation and drug loading[36]. These findings, revealing intricate details of polymer-drug complexes and binding energies, significantly reduce experimental efforts in the design of drug delivery systems.

Molecular docking studies shed light on H-bonding, electrostatic, and hydrophobic interactions at atomic and molecular levels, influencing drug loading and encapsulation efficiency in polymer-based nanosystems[36]. Molecular dynamics (MD) simulations, when integrated with Flory-Huggins theory, provide a powerful approach for predicting drug-loading efficiency in nanoparticle systems. Flory-Huggins theory is crucial for understanding the thermodynamics of polymer-solute interactions, which are key to determining how well a drug can be incorporated into a polymer matrix. By applying this theory within MD simula-

tions, researchers can visualize and quantify how the drug molecules interact with the polymer components of nanoparticles. This method enables the estimation of the miscibility and distribution of drug molecules within the polymer, thereby predicting the efficiency with which drugs are loaded into nanoparticle carriers. This combination of MD simulations and Flory-Huggins theory thus serves as an essential tool in optimizing the design of drug delivery systems, ensuring that they can effectively encapsulate and retain therapeutic agents[37]. The use of Arguslab molecular docking software for analyzing drug behavior in silicon nanocarriers found that larger molecules exhibit lower interaction energy, which is advantageous for loading into these nanocarriers[35].

Assessment of drug release dynamics

The biodistribution, accumulation, and diffusivity of various drug-loaded nanoparticles are critical factors affecting drug release. Modeling drug release from polymeric nanoparticles involves simulating the transport and cellular trafficking of these particles to the target site. These simulations explore the influence of nanoparticle characteristics such as size, surface properties, vascular affinity, and ligand/receptor surface density on transport, cellular trafficking, and consequent drug release within tumor neovasculature[38].

DPD simulations have been employed to study copolymer self-assembly into vesicles and their effects on drug loading and release rates. One instance is the analysis of the assembly mechanism of 'poly (β-amino ester) grafted with polylactide and poly (ethylene glycol) (PAE-g-PEGLA)' copolymers using integrated DPD and MD simulations. This model evaluated the effect of amphiphilic pH-sensitive polymeric vesicles on doxorubicin hydrochloride loading and release, demonstrating that, at neutral pH, higher polymer concentrations resulted in more efficient loading. At pH levels below neutral, poly(ethylene glycol) chains became hydrophilic and protonated, enhancing membrane permeability and promoting drug release[12].

Another study focused on camptothecin loading and release in pH-sensitive amphiphilic copolymers, using integrated DPD and MD simulations. These simulations accurately forecasted the drug loading process into the micelle's hydrophobic core and its interface with hydrophilic regions, closely matching empirical data. The vesicle's swelling and demicellization due to protonation triggered the drug release[39].

The release behavior of 5-fluorouracil adsorbed onto plain and amine-functionalized mesoporous

silica nanoparticles was examined using MD simulations. The release pattern was analyzed based on the first adsorbed layer of 5-fluorouracil. Amine-functionalized nanoparticles released half of the 5-fluorouracil in about 67 nanoseconds, whereas non-functionalized nanoparticles did so more rapidly, in approximately 25 nanoseconds. The diffusion coefficient was higher in plain nanoparticles, aligning with experimental results[34].

These simulation studies are effective in predicting drug release rates, assisting formulators in devising optimal carriers for therapeutic agents[40].

Assessing stability

Achieving maximum drug loading capacity and maintaining micellar system stability are essential for successful nanoparticle formulations. One such example is the role of cetyltrimethylammonium bromide (CTAB) in stabilizing zinc sulphide (ZnS) nanoparticles. Stability is reliant on the concentration of cation-charged cetyltrimethylammonium (CTA^+) ions and their adsorption behavior on the nanoparticle surface. Molecular dynamics (MD) simulations have been primarily utilized. These simulations assess the adsorption behavior of CTA^+ ions on the nanoparticle surface, which is crucial for determining the stability and subsequent release characteristics of the drug-loaded nanoparticles. The computational approach helps in optimizing the concentration of CTA^+ ions to achieve maximum stability and effective drug release[41].

Molecular modeling and Flory-Huggins interaction theory are collaboratively used to predict miscibility and drug-polymer interactions, crucial elements influencing nanoparticle stability.

The Flory-Huggins theory is a thermodynamic framework that quantifies the degree of interaction between different molecular species, such as drugs and polymers. It provides key parameters such as the interaction parameter, which helps in understanding the solubility and miscibility of the components within the nanoparticle system.

Utilizing molecular modeling techniques, such as the group contribution method (GCM) and molecular dynamics (MD) simulations, complements the Flory-Huggins theory by allowing for detailed and specific observations of how drug molecules and polymers interact on a molecular level. These simulations calculate drug-polymer interaction parameters by considering factors such as dispersive forces, dipole interactions, and hydrogen bonding. They also enable the visualization of molecular spatial structures, thereby enhancing the prediction of system stability.

For instance, the compatibility of the chitosan-g-glyceryl monooleate copolymer was predicted using these combined methods. The molecular modeling provided a detailed visual and quantitative analysis of the copolymer interactions, while Flory-Huggins theory offered theoretical backing to understand the thermodynamics of these interactions. The result was a system predicted to be stable, displaying a compact structure, and optimal spherical shape.

Therefore, the integration of molecular modeling simulations with Flory-Huggins theory is pivotal in predicting drug-polymer compatibility, and contributes significantly to the development of stable nanoparticle formulations. This synergistic approach ensures a robust theoretical and practical understanding of the factors that influence the stability of nanoparticle systems[29].

Nanoparticle transportation and interaction with cell membranes

Transporting nanoparticles for drug delivery involves complex processes, including navigating through blood flow, interacting with cell membranes, and cellular internalization[9–14,57]. These steps, compounded by the dense network of blood vessels and the complexity of in vivo transport mechanisms (including cellular recognition, opsonization, internalization, permeability and retention effect, and enzymatic degradation), present considerable challenges. The physical and chemical properties of nanoparticles add to the complexity of understanding these processes. Current experimental tools have limitations in investigating selective targeting and visualizing the delivery mechanism[58,59].

Computational simulation has emerged as a vital pre-screening tool in the development and optimization of nanoparticle formulations at the molecular level, enhancing their performance in biological systems[9,11,24]. For instance, Fullstone *et al.*[8] employed computational fluid dynamics (CFD) to model the blood flow-dependent behavior of nanoparticles, examining their distribution and the influence of fluid dynamics, red blood cells, nanoparticle size, and polydispersity on selective targeting.

Another study utilized dissipative particle dynamics modeling to evaluate the effect of nanoparticle surface modification on protein adsorption and cellular uptake. The simulations indicated that nanoparticles coated with zwitterionic and hydrophilic polymers demonstrated resistance to protein adsorption, thereby affecting cellular uptake. Specifically, zwitterionic polymer-coated nanoparticles

showed increased affinity to cell membranes in low pH environments, enhancing active targeting[10].

Various computational simulations, including MD and Monte Carlo simulations, have explored the interactions between cell membranes and nanoparticles. MD simulations investigate the interaction of nanoparticles with lipid layer biomolecules to establish quantitative structure–activity relationships[42]. Monte Carlo simulations provide insight into the selective interactions of nanoparticles with cell membrane surfaces, binding affinities, and membrane protein expression levels, while DPD simulations study the interactions between lipid bilayers and nanoparticles, analyzing the dynamic behavior of lipid bilayers[15,57].

Atomistic molecular dynamics (MD) simulations play a critical role in elucidating the mechanisms by which nanoparticles interact with and penetrate cell membranes. These simulations provide detailed insights into the molecular interactions between nanoparticles and lipid bilayer components, crucial for understanding how nanoparticles can effectively deliver drugs at the cellular level. For example, a notable study by Zhao *et al.*[27] used atomistic MD simulations to investigate the translocation of gold nanoparticles through a phospholipid bilayer. The simulations revealed how nanoparticle size, coating, and surface charge influence their ability to penetrate cell membranes without causing significant disruption to the membrane structure. This level of detail helps in designing nanoparticles that can efficiently cross cell membranes while minimizing potential cytotoxicity.

A critical aspect of nanoparticle transportation within the vasculature is the phenomenon of margination. Margination refers to the migration of nanoparticles to the periphery of blood vessels, close to the vessel walls, which is critical for effective drug delivery. This process enhances the likelihood of nanoparticle interaction with targeted cells and tissues. The complex interplay of nanoparticle size, shape, and surface properties with blood flow dynamics, influencing how effectively nanoparticles can marginate and subsequently interact with specific sites within the vascular system[74].

The limited understanding of nanoparticle biodistribution has prompted the integration of computational modeling into laboratory research workflows. The physiologically based pharmacokinetic (PBPK) model, for example, has significantly enhanced knowledge of pharmacokinetic mechanisms[24]. Phagocytosis, a crucial factor affecting nanoparticle biodistribution, has been less explored despite its importance. Li *et al.* developed a PBPK model for engineered nanoparticles, investigating the biodistribution kinetics of intravenously administered polyethylene glycol-coated polyacrylamide (PAA-peg) nanoparticles in rats. This model provided a comprehensive view of the phases of nanoparticle biodistribution, including rapid organ distribution, body-wide diffusion, and eventual accumulation in organs rich in phagocytic cells[23,71].

Utilizing computational modeling in nanocarrier development

Development of organic nanoparticles

Organic nanoparticles are crafted using various organic polymers. A significant number of such nanoparticles have already been commercialized, while numerous others are progressing through clinical trials.

Polymeric nanoparticles

Polymeric nanoparticles are a transformative development in biomedicine, characterized by their enhanced drug loading capabilities, biocompatibility, and controlled drug release mechanisms. The intricacies of polymeric systems present challenges in mastering design intricacies and biological interactions. The combination of computer simulation followed by wet lab experimentation has become an indispensable approach in this field.

Computational docking and molecular studies have notably enhanced the bioavailability of curcumin in polymeric nanoparticles. In silico docking analyses have scrutinized the binding energies, interaction dynamics, and affinities of chitosan polymers with curcumin. The process of selecting the most appropriate polymers for nanoparticle formulation hinged on their stable binding modes and strong affinity with curcumin, potentially amplifying its anticancer efficacy[66,72].

In another investigation focusing on copolymeric nanoparticles, atomistic molecular simulations were employed to study the interactions between itraconazole and its polymeric matrix. Specifically, GROMACS, a versatile software package for performing molecular dynamics, was used to simulate the behavior of itraconazole within the nanoparticle environment. The simulations revealed a propensity for itraconazole molecules to accumulate at the water-polymer interface, rather than within the hydrophobic core. This insight is crucial as it influences the drug loading efficiency and the overall effectiveness of the nanoparticle formulation. GROMACS facilitates these detailed simulations by providing tools to examine molecular dynamics comprehensively, including energy minimization and particle interactions, which are essential for understanding drug-polymer relationships within the nanoparticle structure[43].

Physicochemical attributes such as size, surface charge, and hydrophilicity are critical in dictating the biodistribution of nanoparticles. A physiologically based pharmacokinetic model was applied to interpret how these characteristics impact the biodistribution of poly(lactic-co-glycolic) acid (PLGA) nanoparticles. This model enabled the prediction of biodistribution in new formulations, complemented by multivariate regression analysis to forge connections between nanoparticle traits and biodistribution factors[22].

Prodrugs-based nanoformulation

Designing prodrug formulations is focused on enhancing biopharmaceutical, pharmacokinetic (PK), and pharmacodynamic (PD) properties of drugs. Efficient enzymatic or chemical activation mechanisms, crucial for the release of parent drugs, are fundamental in successful prodrug development. Merging innovative molecular modeling with a reasoned prodrug approach is a key trajectory for future advancements[44].

Prodrug nanoformulations are designed to minimize off-target effects and toxicity. For instance, dissipative particle dynamics (DPD) and MD simulations have been utilized to decode the structure and self-assembly of pro-nifuroxazide nanoparticles. These simulations detailed the formation of a three-layered nanoparticle structure, accurately forecasting the particle size[45].

Li *et al.* investigated the self-organization and release pattern of a methotrexate-camptothecin prodrug co-delivery system. Through MD simulation and density functional theory calculations, insights into nanoparticle formation and drug release mechanisms were obtained, showing the stability of the nanoparticles and the controlled drug release in acidic environments[46].

Simulations have also been instrumental in understanding the cellular uptake of cyclodextrin-based nanoparticles for cancer therapy. Molecular docking and MD simulations evaluated the binding affinity of a prodrug complex to cancer cell receptors, suggesting effective cellular uptake through endocytosis[47]. These advancements underscore the vital role of computational modeling in the evolution of nanomedicine, particularly in the conceptualization and refinement of polymeric and prodrug-based nanoformulations.

Polymeric micelles

Polymeric micelles are composed of a hydrophobic core suitable for loading hydrophobic drugs and a hydrophilic shell that enhances stability. The efficiency of these micelles hinges on their high drug loading capacity and their drug release patterns.

DPD simulations have been key in examining drug release from pH-sensitive polymeric micelles. These simulations help clarify the drug release mechanism, the effect of structural changes in the micelles, and how the amphiphilic nature of polymers influences drug release. DPD is particularly useful for modeling the complex, mesoscale interactions and dynamics within polymeric micelles due to its efficiency in handling large polymeric systems, which allows for the exploration of micellar behavior under various conditions, such as changes in pH. For instance, as shown in Fig. 2, the Mesocite module of Materials Studio, a software tool that facilitates the setup and analysis of DPD simulations, has been utilized to study the influence of pH-responsive blocks and the length of hydrophilic blocks on drug release rates. This specific application of DPD simulations demonstrates how computational tools can provide insights into the micellar architecture and its functional response to environmental changes[48].

In another use of DPD, the encapsulation of diverse drugs (beta-carotene and doxorubicin) in amphiphilic copolymeric micelles was simulated. This simulation facilitated the exploration of the interplay between drug distribution and the effect of hydrophobic segments like poly(ethylene glycol)-poly(ε-caprolactone) (mPEG-β-PCL) or poly(ethylene glycol)-poly(ʟ-lactide) (mPEG-β-PLLA) within the micelles. It was observed that both drugs predominantly localized in the core of poly(ε-caprolactone) micelles, whereas in poly(ʟ-lactide) micelles, the drugs were more evenly dispersed, suggesting that poly(ʟ-lactide) hinders drug concentration in the core, leading to more widespread distribution[49].

Furthermore, DPD simulations have been employed to investigate the formation process of drug-loaded copolymeric micelles, guiding the experimental conditions for creating optimized micelles. Simulations indicated that a particular combination of doxorubicin and docosahexaenoic acid (DHA) conjugated with His10Lys10 molecules could self-assemble into a copolymeric micelle with evenly distributed drug. The formation was observed to progress through four stages: dispersion, clustering, formation of small micelles, and the aggregation of these micelles into stabilized, drug-loaded micelles. Experimental results validated these simulation findings[50,69,70,73].

Additionally, the influence of pH levels and block polymer lengths on the loading of doxorubicin molecules into micelles was investigated through DPD simulation. It was determined that self-assembled polymeric micelles were more compact and denser at pH values above 6, effectively trapping the drug inside the core. Below pH 6, with-
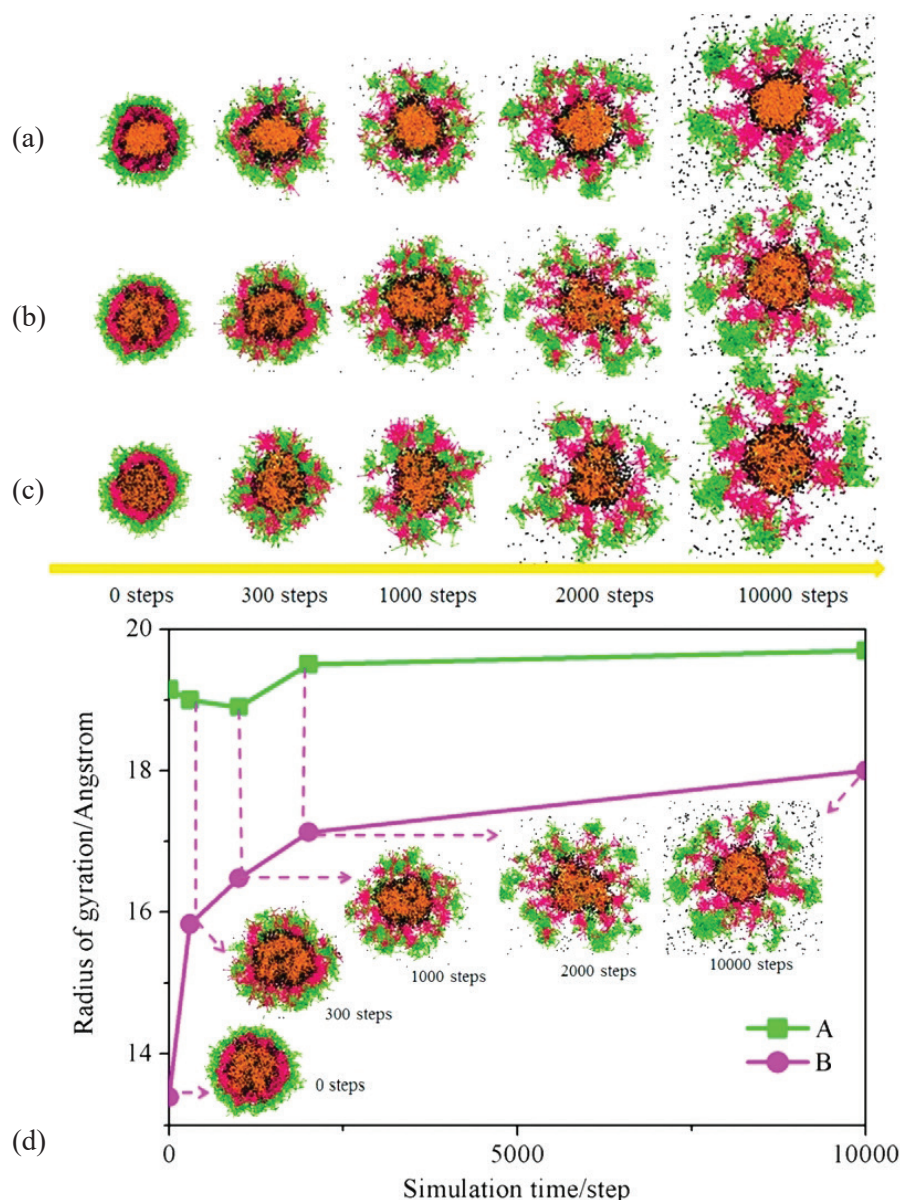
Fig. 2 – *Release mechanism from micelles: (a) In an acidic environment, the pH-sensitive block undergoes protonation becoming more hydrophilic and facilitating the polymer to stretch towards the solvent (0 to 300 steps); (b) The initial step of swelling followed by drug release (300 to 1000 steps); (c) The micelles continue to swell as water molecules diffuse into them, and the pH-sensitive blocks are in fully stretched phase (1000 to 10,000 steps). Reproduced with permission[48].*

out altering the polymer block length, the polymeric micelles showed minimal change. However, modifying the polymer length led to a structural transition in the micelles from dense to more swollen structures[51]. This synergy of experimental and simulation approaches offers an optimal pathway for designing and fine-tuning biopolymers in drug delivery systems to achieve the desired characteristics.

Inorganic nanoparticles

In the biomedical field, inorganic nanoparticles are gaining prominence owing to their stability, targeted drug delivery, high sensitivity, efficient cellular uptake, and low toxicity. Active development of

these nanoparticles is underway, with computational simulations playing a pivotal role in their design and development, offering cost and time efficiencies.

Silver nanoparticles

Silver nanoparticles are widely recognized for their antimicrobial properties and have been incorporated into various biomedical applications[52,53]. Equilibrium molecular dynamic (EMD) simulations have been employed to estimate the viscosity of nanofluids containing silver nanoparticles. This research demonstrated that both temperature and nanoparticle weight fraction significantly affect

nanofluid viscosity, with elevated temperatures leading to decreased viscosity due to accelerated atomic movement[54,68].

Surface functionalization of silver nanoparticles, especially with peptides, is known to enhance their drug delivery capabilities. A computational model was established for poly-L-arginine (poly-Arg30) grafted silver nanoparticles using a pH-responsive constant protonation method. This model revealed that unprotonated poly-Arg30 showed robust adsorption to silver nanoparticles, indicating strong bond formation, while protonated poly-Arg30 displayed weaker adsorption[53].

In silico modeling has been instrumental in elucidating the inhibitory effects of silver nanoparticles on cytochrome P450 enzymes. Using AutoDock 4.2, a software tool for automated docking of ligands to proteins, docking studies identified specific interactions between silver nanoparticles and various cytochrome P450 isoforms. These interactions were further analyzed with quantum mechanics calculations to provide deeper insights into the interaction energies, enhancing our understanding of how silver nanoparticles might interfere with human metabolic pathways[55].

MD simulations have been applied to assess the stability of silver nanoparticles coated with cationic cetyltrimethylammonium (CTA^+). These simulations revealed that a dense CTA^+ molecule layer is essential for nanoparticle stability[56]. Nisin, an antibacterial agent, was conjugated to silver nanoparticles, and MD simulations were used to examine the interaction energy, thereby enhancing the nanoparticles' antibacterial effectiveness[57].

Razavi *et al.* utilized a Lamarckian genetic algorithm in molecular docking to compute the binding energies of various bacteria to silver nanoparticles. The findings showed that certain bacteria, such as *Klebsiella pneumoniae* and *Escherichia coli*, exhibited strong hydrophobic interactions with the nanoparticles, indicating substantial antibacterial efficacy[58].

Studies on the pharmacokinetics and biodistribution of silver nanoparticles of varying sizes in rats demonstrated that smaller nanoparticles primarily accumulated in the liver, whereas larger ones were predominantly found in the spleen and lungs. Physiologically based pharmacokinetics (PBPK) modeling was employed to delineate the pharmacokinetics and potential toxicity of these nanoparticles[21].

PBPK modeling also shed light on the biodistribution of silver nanoparticles, showing that changes in size and surface coating had a minor effect, and that nanoparticles tend to accumulate as insoluble salts rather than as dissolved silver ions[25].

This extensive use of computational tools at various stages of development highlights the crucial role of simulations in propelling inorganic nanoparticle research forward.

Mesoporous silica nanoparticles

Mesoporous silica nanoparticles (MSNs) have emerged as a key focus in the realm of bionanotechnology, owing to their exceptional drug loading capabilities, considerable pore volume and size, adjustable drug release, and potential for surface functionalization. These characteristics render MSNs suitable for diverse applications, including biocatalysis, and gene/drug delivery[59–61].

Elucidating the synthesis process

Molecular dynamics (MD) simulation using atomistic models has provided qualitative insights into the self-assembly process of silica/surfactant structures. Studies investigating the influence of silica molecules on the self-assembly of surfactants, such as decyltrimethylammonium bromide, have revealed that silicate-surfactant interactions facilitate the formation of larger surfactant aggregates and the condensation of silicates[65]. Further, multiscale simulation models have offered more precise insights into the synthesis mechanisms, uncovering the development of hexagonal liquid crystals contingent upon the presence and configuration of silica monomers[62].

Investigating drug loading and release dynamics

Computational models have been expanded to study drug loading and release mechanisms in mesoporous materials. MD simulations, for instance, have clarified how the shape of silica nanocarriers impacts drug release. Comparisons of different shapes (planar and spherical) of silica nanocarriers loaded with drugs like ibuprofen and gemcitabine demonstrated notable variances in drug release, dependent on the bonding strength between the silica and the drug molecules[63].

Another MD simulation explored Schiff-base copolymer grafted MSNs to analyze the adsorption and diffusion of doxorubicin through mesopores. The findings indicated that adsorption was driven by hydrogen bonding between doxorubicin and silanol groups and π-π interactions with benzene rings, influencing drug diffusion and release[64].

Focusing on functionalization and catalytic activity

Research has also concentrated on surface functionalization and catalytic activities of MSNs. Reactive force field (ReaxFF) modeling, in conjunction with experimental NMR studies, has been

utilized to examine the behavior of functional groups within MSNs' mesopores[65]. Computational analyses have delved into the influence of the silanol environment on the catalytic efficiency of amine-functionalized MSNs in aldol reactions, demonstrating how the silanol environment stabilizes zwitterion intermediates and promotes hydrogen bond formation[66,67,73].

Challenges and future directions in computational nanoparticle research

While significant strides have been made in computational nanoparticle research, limitations persist. Anticipated advancements in this field hinge on the development of more realistic models that align closely with experimental data. Current computational efforts are largely qualitative, focusing on aspects like binding free energy, partitioning, and pore formation in membranes. Validating model outputs against experimental data remains a critical step in verifying model precision. Although advanced multiscale models are promising for guiding nanoparticle design, they still depend on experimental data for confirmation and accuracy.

One of the primary technical limitations in computational nanoparticle research is the scale of computational resources required to accurately simulate complex biological systems. The computational cost increases exponentially with the size of the system and the level of detail required, often necessitating simplifications that compromise the model's realism. For instance, atomistic simulations that provide high-resolution insights are typically limited to smaller systems or shorter timescales due to their computational demands. Furthermore, the accuracy of computational models heavily relies on the quality of the input parameters and the assumptions underlying the modeling techniques. Misestimations or oversimplified assumptions can lead to discrepancies between computational predictions and actual experimental outcomes. This is particularly evident in the modeling of nanoparticle interactions with complex biological environments, where the heterogeneity and dynamic nature of biological tissues are challenging to replicate accurately[29,41,43,69].

Understanding nanoparticle behavior under diverse biological conditions remains a challenge. Special emphasis on the external environment is imperative for the development of targeted drug delivery systems, taking into account both extracellular/intracellular environments and distinctions between diseased and healthy tissues. Constructing molecular models that accurately mirror these conditions is crucial, as they significantly affect drug release dynamics. Present computational work is centered on specific cellular uptake mechanisms like direct penetration and phagocytosis[23,24].

To overcome these hurdles, employing hybrid simulation models, integrating experimental and computational methods, extending simulation durations and timescales, and optimizing model calculations are advised. Such a holistic approach promises to deepen understanding and facilitate the more effective creation of nanoparticle-based drug delivery systems.

Concluding observations

The limitations of experimental techniques at the atomic scale have rendered computational simulations indispensable for acquiring a detailed and quantitative grasp of drug delivery systems, particularly in dynamic biological settings. These methods offer substantial benefits by representing millions of atoms and capturing their interactions over extended timescales, from milliseconds to femtoseconds – a level of detail unattainable through traditional experimental methods.

Molecular modeling has become an essential instrument in the intricate design and development process of nanoparticles. As technological capabilities advance, computational simulation is expected to become a fundamental component of nanoformulation development. This integration is particularly critical given the complex and multifaceted nature of these processes.

Despite its increasing significance, the domain of computational simulations in nanoformulation development is still developing, with numerous unresolved questions and challenges. To enhance molecular modeling techniques and improve the characterization of nanotechnology-based drug delivery systems, different strategic directions could be pursued such as development of more accurate force fields, integration of machine learning and AI, multi-scale modeling techniques, enhanced hardware and parallel computing, standardization and validation protocols, and collaborative frameworks. However, given the accomplishments so far, it is clear that large-scale simulations will increasingly play a crucial role in the future of nanoparticle formulation and development. This progress is poised to lead to more efficient, effective, and precisely targeted drug delivery systems.

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