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Advances and Perspectives in Drug Delivery Systems Based on Molecular Dynamics Simulations

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Abstract. The target of Drug Delivery Systems (DDS) is to improve drug bioavailability and reduce side effects, which represents a research focus in modern medicine and pharmacy. Traditional experimental methods have limitations in elucidating low bioavailability and the interaction mechanisms between drugs and carriers. Therefore, this study employs a literature review and case analysis to systematically explore the application of molecular dynamics (MD) simulations in drug delivery systems. Particular emphasis is placed on their unique advantages in nanoparticle design, drug loading, and release mechanisms. This research highlights the progress of MD simulations and further examines the current challenges. It also envisions broad prospects for integrating advanced technologies, such as machine learning and multiscale simulations in the future of drug delivery system development.

Keywords: Molecular Dynamics Simulation, Nanoparticles, Drug Delivery Systems

1. Introduction

Drug Delivery Systems (DDS) represent an innovative form of pharmaceutical administration, enabling precise targeting and control of drug distribution within the body to deliver therapeutics to the intended site at the optimal time. Conventional drug delivery methods frequently face significant limitations, including low bioavailability, poor targeting, uneven distribution within the body, and susceptibility to enzymatic degradation, thereby severely constraining clinical efficacy. Researchers are dedicated to developing novel drug delivery systems that enhance therapeutic efficacy and reduce adverse effects by improving drug absorption, enabling controlled release, and enhancing targeting. Among these, nanoparticle-based drug delivery systems exhibit significant potential due to their unique physicochemical properties—such as large surface area, high modifiability, and distinct interactions with biological systems at the nanoscale, making them a prominent research focus in pharmaceutics and related fields in recent years.

Existing research has primarily focused on the construction of nanomedicine delivery systems and the evaluation of their in vivo behaviour, yet there remains a notable gap in understanding their molecular mechanisms and kinetic pathways. Given that key properties, such as carrier stability, drug loading efficiency, targeting capability, and precise release under physiological conditions, are intrinsically linked to interactions at the atomic or molecular level, a systematic investigation of these molecular-level interactions is urgently required.

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This paper uses a literature review to systematically examine investigations concerning the application of molecular dynamics simulations in drug delivery systems. It aims to explore the molecular dynamics simulations pathways and elucidate the mechanisms of drug loading, release within nanocarriers, and transport within biological environments. This study provides DDS researchers with a comprehensive perspective on the current state of MD simulation applications, revealing their significant potential in accelerating drug development and realizing precision medicine.

2. Fundamental principles of molecular dynamics simulations

Molecular dynamics (MD) simulations serve as a powerful computational tool that simulates atomic and molecular trajectories by solving Newton's equations of motion. This approach unveils the structural, kinetic, and thermodynamic properties of matter at the microscopic level. In the field of DDS, MD simulations are increasingly prevalent, providing atomic-level resolution information that is difficult to obtain through traditional experimental methods. This enables a deeper understanding of drugs, carriers, and biological environments.

The core of molecular dynamics simulation lies in tracking the motion trajectories of each atom within a system by numerically integrating Newton's equations of motion. This process requires precise interatomic interaction potentials, or force fields, to describe the forces between atoms. Tuckerman and Martyna provided a detailed exposition of modern molecular dynamics simulation techniques and applications in 1999. This encompasses Newtonian and Hamiltonian dynamics, non-Hamiltonian schemes, and the Liouville operator [1]. It also addresses empirical force fields and ab initio methods, where force field selection critically influences simulation accuracy. This choice determines the specific method for calculating system energy, thereby affecting the precision of atomic motion simulations. With continuous improvements in computational power and algorithmic optimisation, the temporal scale and system size achievable in MD simulations have approached biologically relevant levels. This enables researchers to analyse conformational ensembles rather than isolated structures. Hospital noted that this theoretical foundation marked a shift in structural bioinformatics from single-structure analysis towards ensemble analysis [2].

3. Nanocarrier design and optimisation

As a core component of drug delivery systems, the structure, stability, drug loading capacity, and release behaviour of nanocarriers directly influence therapeutic efficacy. It holds promise for revolutionising treatments for diverse conditions including cancer, infectious diseases, and chronic illnesses. The behavioural mechanisms of nanomaterials within complex biological systems often involve two or more dynamic in vivo cycles. Notably the circulation, cell membrane penetration, and intracellular transport, along with interactions between drugs and carriers, and between carriers and biological components (proteins, lipids, nucleic acids). Conventional experimental methods struggle to comprehensively observe and deeply understand these processes at the microscopic level. MD simulations play an irreplaceable role in the rational design and optimisation of nanocarriers. They can also provide guidance at the molecular level for material selection, structural assembly, and surface modification.

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3.1. Polymeric nanoparticles and micelles

Polymeric nanoparticles and micelles have garnered attention due to their excellent biocompatibility, biodegradability, and drug encapsulation capacity. MD simulations provide a powerful tool for investigating the self-assembly behaviour, internal structure, and drug interactions of these carriers. For example, Shah and his colleagues used computational analysis to explore the role of hydrophobic blocks in poly(γ-2-methoxyfuran-ε-caprolactone). The results showed that the hydrophobic furan-substituted segments enhanced polymer-drug interactions, potentially increasing drug loading capacity [3]. They further employed MD simulations to guide the micelle assembly process of doxorubicin-doped PEG-b-PfuCL block copolymers. Simulation results confirmed that furan-substituted micelles exhibit heightened polymer-drug interactions. It directly resulted in enhanced drug loading and reduced premature leakage. These findings demonstrate the potential of functionalised polymers for the design of micellar carriers optimised for doxorubicin therapy.

3.2. Carbon nanomaterial carriers

Carbon nanotubes (CNTs) and graphene represent two well-studied classes of nanomaterials in drug delivery research. They have attracted extensive attention in drug delivery due to their high aspect ratios, tunable surface chemistry, and other unique structures, as well as the outstanding physicochemical properties. MD simulations can be employed to investigate the specific mechanisms of drug-material interactions. For instance, Zhao and others utilised MD simulations to determine the effect of carboxyl (COOH)-functionalised carbon nanotubes on the behaviour of doxorubicin [4]. Increasing the proportion of carboxyl groups on the CNT surface successfully enhanced the structural density in the drug-interacting region, thereby improving drug loading capacity and thermal stability. Increased shear stress and reduced molecular mobility suggest a new potential for functionalised CNTs for optimising doxorubicin therapy.

3.3. Metal-Organic Frameworks (MOFs) and inorganic nanoparticles

Metal-organic frameworks (MOFs) and various inorganic nanoparticles are regarded as significant materials in drug delivery. Their features, including highly ordered porosity, large surface areas, and tailorable surface chemistry can assist in controlling drug absorption. Mashayekh and his team have systematically evaluated the potential of MOFs as carriers to enhance the delivery efficiency of cisplatin to cancer cells by combining molecular dynamics simulations with molecular docking techniques [5]. Their simulations showed that cisplatin–MOF complexes displayed greater penetration across model cellular membranes compared to free cisplatin. Simulations further determined an optimal pH of 7.4 for adsorption and interaction, providing molecular-level confirmation of MOFs' viability and advantages as cisplatin nanocarriers.

3.4. Other nanocarriers

MD simulations are increasingly employed to investigate novel drug delivery platforms. Simulating drying processes remains central to understanding drug encapsulation and binding mechanisms. Gosecki et al. applied this method by using MD simulations to evaluate the drug encapsulation efficacy of selected stellate hyperbranched polyglycol structures [6]. This study revealed that two polymers could encapsulate the hydrophobic clotrimazole with 83% efficiency, while the hydrophilic tinidazole bound to surface regions. MD simulations predicted the behaviour of drug-

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polymer complexes and achieved high encapsulation efficiency, providing computationally derived binding mechanisms for drug delivery system design.

4. Drug loading and release mechanisms

MD simulations possess unique advantages in elucidating the molecular mechanisms by which drug molecules bind to carriers, remain stable within them, and release under specific conditions. A thorough understanding of these mechanisms is crucial for designing efficient, controllable drug delivery systems.

4.1. Drug-carrier interactions

Molecular interactions between drugs and carriers are pivotal in determining loading efficiency and stability. MD simulations enable quantitative analysis of these interactions and identification of key binding sites, thereby informing rational carrier material design. For instance, Raffaini et al. employed MD simulations to investigate quercetin adsorption on amorphous silica surfaces [7]. By comparing adsorption processes under varying drug concentrations and hydrated versus dry surface conditions, they identified cross-validated simulation outcomes with FT-IR spectra of quercetin in silica matrices. Favourable non-covalent interactions, including hydrogen bonding and stacking, are necessary for integrating anti-inflammatory agents into biocompatible materials.

4.2. Drug release kinetics and responsive delivery

Controlled drug release constitutes one of the key functions within drug delivery systems (DDS). Molecular dynamics (MD) simulations can elucidate the release pathways and kinetic mechanisms of drugs under varying environmental stimuli, thereby guiding the design of intelligent, responsive delivery systems. Sakai and others investigated the structural and drug release behaviour of the β-cyclodextrin-cyclophosphamide inclusion complex at temperatures between 300 and 400 K by MD, revealing temperature-dependent release characteristics [8]. Cyclophosphamide was released at 400 K, whereas two stable inclusion structures formed at lower temperatures. The β-cyclodextrin-cyclophosphamide complex exhibited increased rigidity and sphericity, both of which decreased with rising temperature, thereby elucidating the mechanism of temperature-responsive drug release at the molecular level. Raffaini et al. employed MD simulations to investigate the drug migration rate of 5-fluorouracil (5-FU) within β-cyclodextrin (β-CD) host-guest complexes at varying stoichiometric ratios. They discovered a two-step release mechanism in the 1:2 β-CD/5-FU complex: rapid release of exposed drug and slow release of encapsulated drug [9]. These cases not only reveal complex release pathways but also highlight the influence of drug concentration and carrier composition on kinetics.

5. Overcoming biological barriers and targeted delivery

Overcoming complex biological barriers to achieve precise targeting of pathological sites is another challenge. Cell membranes, the blood-brain barrier, and tissue interstices are usually regarded as critical barriers. MD simulations primarily provide molecular-level details concerning interactions between nanocarriers and biological membranes, penetration mechanisms, and recognition of targeting ligands.

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5.1. Cell membrane penetration and interaction

For drug entry into cells, interactions between nanocarriers and cell membranes are a critical step. MD simulations can provide detailed modelling of the sequential events in these processes. Nanoparticle approaches, adsorption, penetration into lipid bilayer membranes, and other steps can all be studied with the assistance of MD. Islam et al., using coarse-grained MD simulations, investigated the nanobiomechanics of targeted delivery of the corticosteroid drug mometasone furoate to the alveolar air-water interface [10]. This simulation revealed that drug entry into the pulmonary surfactant monolayer induces concentration-dependent surface tension changes and reduces diffusion within larger clusters, providing insights for corticosteroid delivery to the alveoli.

5.2. Targeting and biocompatibility

Achieving precise targeted drug delivery can significantly enhance therapeutic efficacy while reducing side effects. MD simulations can aid in optimising the design of targeting ligands and evaluating the biocompatibility of nanocarriers. Jiang et al. elucidated the mechanism by which a folate-based carbon nanotube drug delivery system targets folate receptor alpha, confirming that drug loading mitigates the impact of the CNT-folate linkage on the depth of folate insertion into the receptor pocket. This provides novel insights for designing targeted nanomedical delivery systems [11]. Furthermore, hybrid cell membrane-coated nanoparticles (Dox-Por@TRM), assembled under MD simulation guidance, achieved specific recognition of 4T1 cells and prolonged circulation time. This biomimetic strategy leverages the natural targeting and immune evasion properties of cell membranes, with MD simulations providing crucial insights for optimising membrane composition and structure [12].

6. Discussion

To advance current research, future investigations should focus on the following areas: deepening the integration of machine learning with MD simulations, which requires the intelligent design and optimisation of DDS. For instance, employing ML to predict drug-carrier interactions, drug release kinetics, and in vivo pharmacokinetic parameters could significantly shorten development cycles. Strengthening synergies with experimental techniques to foster close integration between MD simulations and advanced experimental methods, such as cryo-electron microscopy, nuclear magnetic resonance, and single-molecule fluorescence spectroscopy. This integration involves validating and calibrating simulation results with experimental data while using simulation outcomes to guide experimental design, thereby establishing a virtuous cycle of computation-experiment-computation.

7. Conclusion

This paper explores the applications of MD simulations in the field of DDS. The research highlights the pivotal role of MD simulations in optimising the design and assembly of nanocarriers. On the one hand, MD simulations can reveal the self-assembly behaviour, structural stability, and interactions with drug molecules of various nanocarriers—such as polymeric colloidal bundles, carbon nanotubes, metal-organic frameworks (MOFs), liposomes, and biomimetic nanoparticles—at atomic or coarse-grained levels. On the other hand, MD simulations provide profound insights into drug loading, release mechanisms within nanocarriers, and transport mechanisms within biological environments.

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MD simulations not only provide quantitative insights into drug-carrier interaction forces and identify key binding sites but also model drug release kinetics under varying physiological conditions. Furthermore, in overcoming biological barriers, MD simulations can model interactions between nanocarriers and cell membranes, penetration mechanisms, and targeted ligand recognition, providing molecular-level details for designing drug delivery systems (DDS) with enhanced bioavailability and targeting.

This paper has certain limitations. The present study relies solely on secondary data and relevant literature, lacking empirical data to substantiate its findings. Future research should further explore the application of MD simulations to provide more reliable data-driven evidence for optimising parameter sets in processes such as nanocarrier refinement.

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