APPLICATIONS OF SIMULATION STUDY IN DESIGN OF DRUGS AND DRUG DELIVERY SYSTEM

Abstract

In the field of computer-aided drug discovery and design, the molecular simulation approach is a reliable technique that is used *in silico* to investigate interactions between various species within various systems at the atomic level and to answer questions that cannot be detected and answered experimentally. The molecular simulation approach, which is employed to investigate the interactions between various species inside various systems down to the atom level and to address issues that cannot be detected and resolved experimentally, is a reliable technique when it comes to computer-aided drug discovery and development. Many different forms of drug delivery systems (DDSs), including medications, pharmaceuticals, DNA, bilayer membranes, polymers, proteins, peptides, nanoparticles, and other materials, are visualized using MD simulations. This chapter discusses the method of molecular simulation and how it is used in the creation of pharmaceuticals and drug delivery systems.

Keywords: Simulation, drug design, drug delivery system, computer-aided, nanoparticles

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I. INTRODUCTION

In the past 10 years, a new field called "computational pharmaceutics" has emerged that blends artificial intelligence and multi-scale modelling methods into drug delivery systems, with the potential to fundamentally alter the way that formulation development is now done. Comparable approaches have become more common in pharmaceutical research thanks to the exponential rise in computing power. The use of computational tools can speed up laboratory research and give quick, precise evaluations of a drug's effectiveness in a specific carrier.

In order to comprehend molecular structures, pharmaceutical drug delivery systems model atomic molecule behavior using molecular dynamic simulations (MDS). MDS may be used to assess the physical properties of drug/excipient combinations without expensive research. Recently, there has been a lot of interest in isotropic lipid-based nanocarriers as possible transporters for materials that cannot be dissolved in water. In order to understand the internal microstructure of lipid-based delivery systems and drug localization, MDS may be a useful technique.

II. MOLECULAR DYNAMICS SIMULATION

Since its initial introduction more than 40 years ago, molecular dynamics (MD) simulation has been used in a range of study fields, and in some cases, it has developed into a new tool for investigating a particular problem. It is still our experience that the pharmaceutical industry lacks a general understanding of what can and cannot be done for studying solubility using computational methods, as well as the reasons why. This is true even though there have already been many excellent reviews on the technical and application sides of MD. Additionally, we compare MD briefly to a few other methods, such as continuum-based models like COSMO and Monte Carlo methods inside the grand canonical ensemble.

The physical interactions that occur between atoms and molecules are referred to as the force field in a simulation or computer experimentas seen in figure 1.
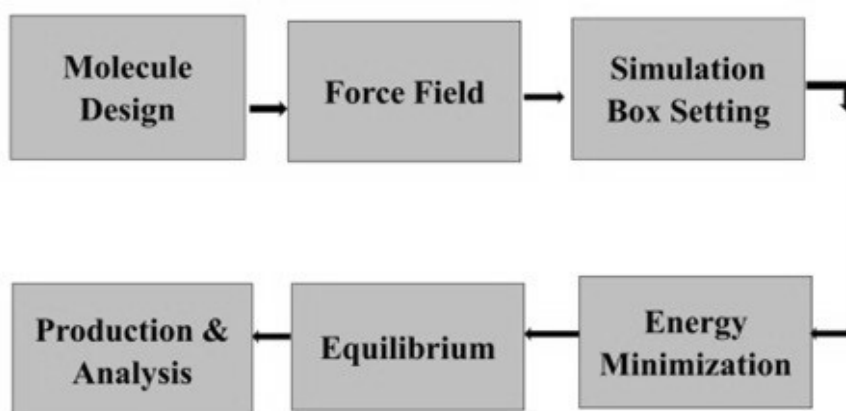

Figure 1: Simulation Study

General Steps for Performing Molecular Dynamics Simulation Study:

Several steps include:
- Initial Geometrics to produce Trajectories, PDF Files, and Topology Files
- Simulation setup for atom, molecule, box, and molecule fitting preparation
- Energy Minimizations to minimize thermodynamic interaction and set up energy molecule arrangement.
- MD simulation for Record Coordinates and Simulation Production
- Analysis of intermolecular interactions and molecule and system properties

III. SOFTWARE FOR SIMULATION STUDY

It takes a lot of work and the cooperation of specialists from other domains to develop computer programs that are appropriate for molecular simulations. Thankfully, a concerted effort by scientists from around the world has produced a number of open-source and for-profit software that is highly competent and successful. Materials Studio, Marvin, PRODRG, Swiss Param, ATB, MKTOP, Avogadro, and other programs and online platforms are used to independently construct molecules, calculate force field parameters, analyze data, and visualize results (e.g., visual molecular dynamics, PYMOL, CHIMAERA).

These algorithms produce dynamic results for simulated systems and offer crucial information on fundamental characteristics of high-quality delivery systems. These software programs, however, come with significant limitations that make use of them impossible.

Some Commonly Used Molecular Dynamics Simulation Software are:
- GROMACS
- NAMD
- DESMOND
- AMBER
- ACEMDable1. Commonly Used Molecular Dynamics Simulations Software Available for Use

An Optimal Carrier for Targeting Drugs should have the Following Characteristics:
- Restricted drug distribution to the target area, organ, tissue, cell, and compartments
- Undergoing capillary-level distribution;
- Prolonged control of drug localization;
- Drug transport primarily to target cells, such as tumor cells;
- Controlled drug release rate;
- Drug release without significantly impairing biological activities;
- Therapeutical concentration of drugs at the desired molecular target;

In this context, the MD simulation is an effective technique that has been widely applied to assess the performance of complex nanoscale systems that link several areas of cell biology and materials research. In addition to its outstanding ability to assess the thermal and mechanical properties of nanostructures, the MD technique also makes it possible to get a deeper knowledge of the interatomic interactions in nano-sized complex systems integrating biomolecules. In present, the MD simulation of the encapsulation processes was performed

using the Large-Scale Atomic/Molecular Simulator (LAMMPS) software (Ver. March 2018). In previous studies, the interaction characteristics of hydrogen and oxygen atoms in water molecules (TIP3P) were obtained using the well-known force field CHARMM27, which is often used in drug delivery models.

IV. MOLECULAR SIMULATION USES IN DRUG DELIVERY SYSTEM

A typical molecular dynamic (MD) simulation that bases itself on Newtonian motion mechanics and treats atoms as the smallest unit is known as an "all-atom simulation." The empirical force field describes how atoms interact with one another. According to the Boltzmann distribution law, the computer selects the starting velocities at random for each atom in the system, solves the equations of motion numerically to find the velocities and coordinates at each given moment, and then performs the simulation of macroscopic characteristics.

1. **Lipid Bilayer Drug Diffusion and Penetration:** The bioavailability of a medicine is significantly influenced by its capacity to cross the lipid bilayer membrane. According to the Meyer-Overton rule, hydrophobic medicines are lipophilic and easily traverse lipid membranes. To determine hydrophobicity and lipophilicity, count the number of hydrophobic and lipophilic sites. Molecular simulations can also provide trustworthy information on the dynamics and structure of bilayers as well as the process of channel creation.

2. **Drug Solubility:** High concentrations of medications with high solubility are present in the fluids of the stomach and intestine, which should enhance medication absorption. Furthermore, differences in medicine solubility brought on by changes in the pH and salt levels in the gastrointestinal system may only be fully explained by molecular simulations.

3. **Carrier-Drug Miscibility:** Many carrier molecules (excipients) are used to enhance the solubility of poorly soluble drugs or maintain drug supersaturation. The choice of such excipients can be aided by techniques for assessing drug-excipient interactions and molecular simulations. Excipients are often substances that interact physically with drug molecules.

4. **Drug Crystallization:** Drug molecules in a range of oral dosage forms, in addition to medications that are poorly soluble, have the potential to crystallize inside the body. Because crystalline chemical forms of a substance do not absorb as well as amorphous versions do, excipients that prevent crystallization are utilized in pharmaceutical formulations. The major focus should be given to the effective coarse-graining processes in crystal modeling, which are systematic but aggressive growth produced by atomistic simulations with adequate parameterization.

5. **Drug Loading and Release:** In the context of carrier-mediated drug release, the terms "drug loading" and "drug release" are used to denote, respectively, how the drug is absorbed into the carrier and subsequently released into the body. To reroute the flow of drugs in a different direction, the environment must be changed. Particularly if it involves

the creation of drug excipient nanostructures, molecular simulations can accurately describe the drug's loading or release process.

6. **Bloodstream Behaviour and Coronal Protective Polymer:** Gao et al. (2020) determined that the best method for modeling nanoparticle transport in the dysfunctional tumor vasculature was computational fluid dynamics (CFD), a discretized continuum model that was described and used to model nanoparticle behavior in the bloodstream and the impact of size and shape. Using experimental analysis and MD, it was determined how two protective polymers, PEG and poly-sarcosine, interacted with a collection of circulatory proteins.

7. **Controlled Release and Drug Loading**: Numerous researchers have investigated the possibility that various types of nanoparticles might store medications and release them in response to external activation. The chemicals being studied are frequently hydrophobic, non-polar, and located in a non-polar zone. Different drug loading issues have all been modeled for liposomes and polymersomes conveying their drug payload. Hydrophobic drugs in the liposome membrane, carbon nanotubes, nanographene, peptide carriers, PAMAM dendrimers, polymeric nanoparticles, and micelles are some of the issues that need to be addressed. Doxorubicin has been examined with 5-fluorouracil, cucurbitacin, carmustine, chalcone, picoplatin, porphyrins, ibuprofen, paclitaxel, and albendazole even though it is the most frequently recommended treatment in these model systems. The purpose of these nanoparticles was to release their therapeutic payload in reaction to a pH change.

Some other Examples are:

- Felodipine with HPMC
- Phenytoin with polymer
- Paclitaxel in DPPC bilayer under shock waves and nanobubbles
- Phenytoin with HPMCAS
- Danazol in simulated GI Environment
- Phenytoin crystal
- Doxorubicin on pristine graphene (PG) and graphene oxide (GO) nanocarriers

V. CONCLUSION

Researchers have investigated many options for using molecular modeling methods to evaluate medication delivery systems. According to what we know, many free energy estimates presented in the literature were simulated with a single drug, ignoring the drug-loaded media. These computations might be used in this method to gather crucial information.Semi-quantitative information may be obtained on a drug's drug release, solubility, loading capacity, etc. into a particular DDS.A lot of DDS development aspects may be acquired by employing molecular simulation. This method is applicable to new DDS systems. They present a fantastic opportunity for developing drug delivery devices that might benefit from molecular dynamics simulations.

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