S.N. Koteswara Rao G.
Rajasekhar Reddy Alavala *Editors*

Applications of Computational Tools in Drug Design and Development

Springer

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Dedicated to all the researchers, faculty, and students
May this book serve as a valuable resource in your journey toward transforming computational insights into therapeutic breakthroughs

Preface

The world of drug discovery and development is a complex, multifaceted field that addresses the pressing challenges in disease treatment. As scientific understanding advances and technology progresses, the integration of computational tools has become increasingly vital, offering new dimensions of insight and precision to researchers. Initially focusing on drug discovery, the computational tools have now amalgamated every aspect of drug discovery and development, including drug discovery, drug delivery, biopharmaceutics, and pharmacokinetics, as well as pharmacology and toxicology. Not many books touch on all of these aspects. Offering a broad perspective, this book explores the computational tools utilized in every phase of drug discovery and development.

Chapters 1–10 of the book delves into applications of computational tools for drug delivery. This part covers application of computational tools for preformulation studies as well as use of design of experiments (DoE) software for optimizing the formulation parameters. Another emerging area of focus is the delivery of drugs to the lungs. The Chap. 7 focuses about computational fluid dynamics and is used to simulate the flow of drug aerosol in the respiratory track and its application in the design and optimization of aerosol-based delivery systems. Likewise, the use of simulation to analyze and optimize key parameters in the pharmaceutical die filling process is discussed in this part.

Chapters 11–19 of the book explores the computational tools for predicting biopharmaceutical as well as pharmacokinetic parameters. Detailed in this part are computational tools for the prediction of solubility, advances in computational prediction of absorption as well as permeation, and forecasting protein binding using computational tools. Also included in this part is a detailed explanation about visualizing and understanding the interactions between drug molecules and excipients using simulations and how this information is used for the selection of best excipient under the given conditions.

Chapters 20–27 focuses on specific therapeutic areas. Through the mechanistic understanding of diseases such as Alzheimer's, diabetes, atherosclerosis, and cancer, this section highlights how computational tools such as QSAR, pharmacophore mapping, docking, and homology modeling as well as network analysis are being

used for design of better drugs. The design of drugs against epilepsy and hypertension is also included in this part. The final chapters explore drug discovery and computational strategies in the context of multidrug-resistant tuberculosis and the network pharmacology approach to uncover the pharmacological mechanisms of natural products. Drug repurposing, highlighted during COVID, although practiced much before it, in the treatment of cancer is also discussed in this part.

This book offers a holistic view of multiple computational tools used at various stages of drug discovery and development. It will be a valuable resource to researchers and students working in this field.

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Foreword

The book *Applications of Computational Tools in Drug Design and Development* is a pleasant blend of computational methods employed in both drug discovery and drug development. It covers how computational methods can be used at all stages in the drug discovery and development process. There are not many volumes that have been published to date that comprehensively cover how *in silico* methods are used in drug discovery and development, and therefore, this volume will be welcomed by all those working in drug discovery and development.

Understanding the mechanism of action of a drug is central to the development and design of new drugs. A variety of experimental methods is used to unravel the mechanism of action of drugs. The use of computational tools like network analysis (STRING, Cytoscape, DAVID, etc.) and molecular modeling tools like docking, QSAR, receptor-based pharmacophore mapping, etc. to understand the pathological mechanisms of anti-Alzheimer agents and drugs used for the treatment of epilepsy and atherosclerosis has been illustrated in Chaps. 20, 22, and 24.

Chemoinformatics, which combines concepts and methods in chemistry, computer science, and information technology, is used to streamline the process of identifying and developing new leads. The tools of chemoinformatics for storage, analysis, visualization, and interpretation of chemical data, and their significance in drug discovery and development are covered in Chap. 9.

Drug likeness aims to predict how promising a molecule is to be developed as a drug. Drug likeness as embodied by Lipinski's rule-of-five has been a guiding principle to identify molecules that are most likely to succeed as novel therapeutic agents. Tools to assess drug likeness have been described in Chap. 19 titled "Recent Advances in Drug-Likeness Screening by Using the Software and Online Tools."

In silico approaches have revolutionized drug discovery by decreasing the time to identify hits, optimize leads, and develop a clinical candidate. The use of *in silico* methods like molecular docking, molecular dynamics (MD) simulations, QSAR, and protein structure determination (homology modeling) to identify new targets and to decipher drug receptor interactions coupled with the prediction of ADME attributes have been exemplified in Chap. 21 in the design of novel antidiabetic agents, and in Chap. 25 in the design of novel antihypertensive agents.

The safety aspect of a drug is an integral part of the drug design process, and the accurate prediction of toxicity helps mitigate the risk associated with the appearance of life-threatening effects during preclinical or clinical studies. Toxicity databases such as ToxCast, ACToR (Aggregated Computational Toxicology Resource), and PubChem can be queried to assess the potential toxicity of known or structurally related substances. Additionally, toxicogenomics tools like GeneGo (MetaCore) and pathway analysis tools, along with in silico toxicity prediction platforms such as ADMET Predictor, the Tox21 collaboration, and DEREK Nexus, can be used to evaluate compound toxicity across multiple biological endpoints. Some toxicity prediction tools are covered in Chap. 16.

Repurposing an existing therapeutic for a new medical condition has several key advantages, such as reduced time to bring the drug to market, since the safety profile of the drug is already established. Viral-based therapies like gendicine, oncorine, and imlygic are examples of therapies that have been repurposed for cancer treatment. These examples and the initiatives by the National Center for Advancing Translational Sciences (NCATS) are covered in Chap. 23 titled "Modern Computational Intelligence Based Drug Repurposing for Cancer."

The appearance of drug resistance across various therapeutic segments is posing serious threats to public health in terms of failure of treatment, development of chronic infections, escalation in the cost of treatment, and narrowing the options available for treatment. The appearance of MDR, XDR, and TDR-TB is creating havoc worldwide in the management of this disease. Chapter 26 on "Drug Discovery and Computational Strategies in Multi-Drug-Resistant Tuberculosis" attempts an overview of various computational strategies, like structure-based and ligand-based, that have been used in the development of new drugs for the treatment of MDR-TB.

Natural products, with their diversity of chemical structures, have been the founding structures on which many therapeutic agents have been designed. The vast untapped biodiversity found in marine ecosystems, tropical rainforests, and the animal world holds the promise of discovery of novel compounds with unique therapeutic attributes. Chapter 27 titled "The Network Pharmacology Approach to Uncover the Pharmacological Mechanism of Natural Products" expounds a multidisciplinary approach based on systems biology and polypharmacology.

After the target has been identified and validated, hits recognized, and leads optimized, preclinical studies that evaluate the solubility, safety, efficacy, drug binding, and pharmacokinetics of lead compounds in laboratory and animal models prior to human testing is conducted. All these aspects are covered in Chaps. 11, 12, 13, and 15. A pivotal aspect of preclinical drug development is the assessment of solubility of the drug candidate. This is essential for formulation design and satisfactory pharmacokinetics. The shake flask method is the gold standard for measurement of solubility; however, quantum mechanical calculations based on DFT, molecular dynamics simulations, QSPR, and machine learning models offer cheaper and accurate ways to model solvation energy. These computational tools are covered in Chap. 11 titled "Computational Tools for Solubility Prediction." Along with solubility, another fundamental theme in preclinical studies is the prediction of absorption, distribution, metabolism, and excretion (ADME) of the drug. Understanding

absorption is essential for predicting a drug's bioavailability, its dosing regimen, and potential effectiveness. Simcyp, GastroPlus, SwissADME, and QikProp are some of the finest tools used for prediction of ADME attributes; these could have been covered in depth along with the other methods described in Chap. 12 titled "Advances in the Computational Prediction of Absorption Prediction of Pharmaceuticals." The amount of drug available for interaction with the target is dictated by the fraction bound/unbound (free) to plasma proteins (e.g., albumin, a1-acid glycoprotein, lipoproteins, etc.) and is a key parameter that is studied in the preclinical phase of drug development. Computational tools used to study ADME, described above, have modules to assess the fraction of drugs bound to plasma proteins. Case studies of how computational methods have been used to optimize protein binding and hasten the drug development process are elucidated in Chap. 13 titled "Protein Binding Prediction by Computational Methods." Biopermeability studies are linked with the prediction of drug absorption and are used to understand how well a drug will cross biological membranes to enter systemic circulation. Poor permeability may necessitate modifications in the chemical structure or alterations in the formulation development. The use of advanced molecular dynamics simulations to predict the bioavailability of pharmaceuticals and its relationship to experimental data has been discussed in Chap. 15.

One of the important stages in drug development is formulation design. In this phase, the focus is on developing a stable, effective, and safe formulation that can be used in human clinical trials. Decisions must be made about the dosage form, whether tablet or injection or any other, and the method of delivery. Computational methods for design of the formulation and mode of delivery—oral, ophthalmic, parenteral, or inhalation—are covered in Chaps. 1, 2, 8, and 10. There are several challenges in the delivery of drugs to the lungs. Factors such as the design of the device, formulation aspects like particle size, dose control, and patient competence all dictate how efficiently the drug is delivered to the lungs. Computational fluid dynamics (CFD) has played a significant role in the aerospace industry and is now making a deep impact in the design and optimization of inhalers, in formulation design (Chaps. 3 and 7), and in the die filling process during tablet compression (Chap. 6). Exhaustive simulations can be conducted to get insights into airflow patterns, particle behavior, and sites of drug deposition within the respiratory system.

The underlying relationships between the dependent and independent variable in a process can be understood by Design of Experiments (DOE). How DOE can be used to optimize the effectiveness of drug delivery systems has been well explained in Chap. 5 titled "Design of Experiments: Understanding Optimization."

A significant percentage of the excipients in pharmaceutical formulations are polymers—natural, synthetic, biodegradable, or mucoadhesive. Computational methods (Chap. 18) are used to understand how a formulation chemist can select the "right" polymer to avoid drug-polymer interactions that could limit the stability, release, or bioavailability of the drug.

All drug discovery programs begin with target identification and target validation. Discussion of this facet of drug discovery, which is missing in this volume, may be covered in a future edition of this book.

In essence, this volume gives a comprehensive insight into the numerous computational methods and tools that are used in various stages of drug discovery and development. This volume would benefit both the novice and experienced pharmaceutical researchers and scientists, clinical researchers, medical professionals, graduate students in a drug discovery program, and the regulatory agencies and professionals.

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We are profoundly grateful to all the **contributing authors** whose dedication, expertise, and commitment to advancing knowledge have enriched this book. Their collective efforts have made this endeavor possible, and we deeply value their contributions.

Finally, we acknowledge the support and encouragement of our families, colleagues, and friends, whose belief in this project has been a source of motivation throughout this journey.

Regards
Dr. S. N. Koteswara Rao G.
Dr. Rajasekhar Reddy Alavala

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Chapter 1
Computational Simulation of Drug Delivery at the Molecular Level

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Abstract Computational simulations at the molecular level are crucial for advancing drug delivery systems by providing insights into drug-receptor interactions, permeation across biological barriers, solubility, stability and conformational changes. Techniques such as molecular modeling, molecular docking studies, molecular dynamics (MD) simulations, quantum mechanics/molecular mechanics (QM/MM) simulations, and free energy calculations play key roles. Molecular modeling predicts structures, conformations, and properties essential for drug efficacy. Docking studies forecast interactions and binding affinities, guiding lead optimization and toxicity assessment. MD simulations reveal drug behavior, stability, and interactions patterns. QM/MM simulations accurately model active sites and chemical reactions. Free energy calculations predict binding affinities and thermodynamic properties, enhancing our understanding of drug receptor interactions. These techniques optimize drug design, pharmacokinetics, and pharmacodynamics and targeted drug delivery systems. Visualization and analysis tools help interpret complex interactions, facilitating effective therapeutic interventions. Computational simulations span development stages, from design to clinical trial simulations, providing a robust frame work for safer and more effective pharmaceuticals. *In-silico* model accelerate drug discovery, reduce animal testing, address ethical concerns, and improve development pipeline efficacy.

Keywords Molecular modeling · Molecular Docking studies · Molecular dynamics simulations · Quantum mechanics/molecular mechanics simulations · Free energy calculations · Drug-receptor interactions · Drug solubility and stability · Pharmacokinetics · Pharmacodynamics · *In-silico* drug discovery

1.1 Introduction

The therapeutic success of any drug molecule is based on its therapeutic action and therapeutic action purely based on drug pharmacokinetic and pharmacodynamics characteristics. The drug therapeutic action of a drug mole follows a sequence of process such as (i) Administered drug absorbs through a bio-membrane, based on its physicochemical properties (ii) Distributes through various biological membrane and reaches the site of action (iii) Binds with receptor and elicits the therapeutic action. The effective therapeutic action is based on drug delivery system, interaction of drug with various biological components and membranes, binding with a receptor and occupying enough number of receptors, this depends on drug concentration at site of action. Molecularly various factors influencing therapeutic action are release of drug molecule from drug delivery system, release drug possess a suitable conformation, absorption and distribution of drug molecule with the same conformational characteristics, structural similarities of drug to the receptor, nature of binding, binding integrity and stability, and binding affinity with the active site of receptor. The therapeutic failure or success of a drug molecule based on interaction of drug molecule with biological system at atomic or molecular level [1–5].

Computational simulations of drug delivery at molecular level are the tools for model and analyze the interaction between drugs and biological system at atomic or molecular scale. The various computational simulations of drug delivery at molecular level are molecular modeling, docking studies, molecular dynamic (MD) simulations, quantum mechanics/molecular mechanics (QM/MM) simulations, free energy calculations and visualization and analysis [6–8].

Researchers captures the structural and chemical properties of the drug molecule with the help of molecular modeling by the help of various software tools example MD, QM/MM simulations to build the models of drug molecules and biological target such as a protein receptor or nucleic acids. Prediction of preferred orientation and conformation of drug molecule when bound to its target site establishes by docking studies with the help of software packages that simulate the interaction between drug molecule and the receptor binding site. The dynamic behavior and interaction of drug molecule with biological system over time is studied with the help of MD simulations. MD simulation allows researcher to observe molecules move and interact within a biological environment by solving Newton's equation of motion to track the positions and velocities of the molecules in the biological systems. QM/MM simulations are combination of quantum mechanics calculations and molecular mechanics calculations. These simulations are for calculation of a small region of the system such as the active binding site on a receptor and allows researcher for accurate modeling of chemical reactions and interactions that occur at the molecular level. Free energy calculations are applicable to predict the binding affinity between a drug molecule and the target receptor and are aims to estimate the thermodynamic properties of the drug-receptor interaction, such as binding free energy; this can provide insights into the strength and specificity of interaction. Finally, researchers analyze the simulation results to gain insights into the mechanisms of drug binding, drug release, and any conformational changes that occur in the biological system upon drug binding. Visualization tools help researchers visualize and interpret the complex molecular interactions observed in the simulations. Overall, computational simulations of drug delivery at the molecular level plays a crucial role in drug discovery and development by providing valuable insights into the mechanisms of drug action and helping to design more effective and targeted therapeutic interventions.

These simulations at molecular level are offering myriad of applications across various stages of drug development and therapeutic implementation. In drug design and optimization, these simulations facilitate molecular docking to predict drug-receptor binding, optimizing affinity and specificity, while also elucidating structure-activity relationships to enhance drug efficacy. For pharmacokinetics and pharmacodynamics (PK/PD) simulations predict drug absorption, distribution, metabolism, and excretion (ADME), guiding dosing regimens and minimizing toxicity. In the design of nanoparticles and carriers, simulations aid in creating efficient drug delivery systems like nanocarrier and controlled release systems, ensuring targeted and sustained drug release. Additionally, they predict drug resistance mechanisms, informing the design of next-generation therapeutics. Personalized medicine benefits from patient-specific simulations that predict individual responses,

optimizing treatment plans; safety assessment is enhanced by predicting off-target effects and toxicities early in development, and understanding potential carcinogenicity and genotoxicity. Biophysical insights from simulations reveal the molecular mechanisms of drug action, adding therapeutic understanding. Simulations also streamline clinical trial design through virtual trials and modeling population variability, reducing trail costs and time. By providing *in-silico* models, computational method reduces the need for animal testing, addresses ethical concerns. Finally, complex disease modeling with multi-scale simulations integrates molecular, cellular, and tissue-level data, supporting the development of comprehensive treatment strategies for diseases such as cancer and diabetes. These diverse applications underscore the pivotal role of computational simulations in advancing drug delivery and therapeutic outcomes [6].

1.2 Computational Simulation Models

These are used to produce more effective and safer drug molecule by modeling and analyzing drug molecule interactions on molecular level with the use of advanced computer models. This approach aims to optimize drug design by enhancing binding affinity and specificity to target receptors, understanding the ADME process and uncovering mechanism of drug action and resistance. The models are as follows (1) Molecular Modeling (2) Molecular Docking Studies (3) Molecular Dynamic (MD) simulations (4) Quantum Mechanics/Molecular Mechanics (QM/MM) Simulations (5) Free Energy Calculations (6) Visualization and Analysis [9].

1.2.1 Molecular Modeling

This plays very important role in computational simulation of drug delivery at molecular level and it allows researcher to explore and optimize various aspects of drug delivery at molecular level by (1) Molecular structure prediction (2) Docking studies (3) Quantitative Structure-Activity Relationship (QSAR) (4) Molecular Dynamic Simulations (5) Drug Carrier Design and helps to accelerate the drug discovery and development process [10–12].

1.2.1.1 Molecular Structure Prediction (MSP)

MSP is the essential component of molecular modeling in the context of computational simulations of drug delivery at molecular level and plays very important role in molecular modeling by providing insights into drug-receptor interactions, physicchemical properties, formulation design, metabolite prediction, and drug transport across biological barriers. Molecular structure prediction contributed to the drug

delivery by (1) Conformational analysis (2) Drug-receptor interactions (3) Prediction of physic-chemical properties (4) Formulation design (5) Prediction of metabolite structure (6) Assessment of drug transport across biological barriers [13, 14].

(a) Conformational Analysis: This analysis in molecular structure prediction identifies the most stable and biologically relevant shapes of drug molecules, crucial for their optimal interaction with targets. Though computational simulations, it ensures that drug adopt conformations that enhance binding affinity and specificity. This analysis aids in predicting pharmacokinetic and pharmacokinetic properties, improving drug efficacy and safety. Thus conformational analysis is essential for designing and optimizing drug molecule for effective delivery.
(b) Drug-Receptor Interactions: These are vital for understanding the drug binding with its target, and guiding the design of molecules with optimal therapeutic efficacy. Computational simulation models these interactions to predict binding efficacy and specificity, aiding in the identification of potent drug candidate. Thus, studying drug-receptor interactions are crucial for developing effective and safe drug delivery system.
(c) Prediction of Physico-Chemical Properties: These are essential for assessing a drug's solubility, stability and permeability, which directly impact its bioavailability and therapeutic efficacy. Computational simulations provide accurate predictions of these properties, guiding the optimization of drug candidates for better performance. By understanding these attributes, researchers can design drugs that are more effective and safe. Thus, predicting physic-chemical is crucial for successful drug delivery and development.
(d) Formulation Design: It ensures that drug candidates are delivered in stable, bioavailable, and effective form. Computational simulations predict how different formulations affect drug release, absorption, and stability, guiding the selection of optimal drug delivery systems. This integration helps translate molecular properties into practical therapeutic applications. Thus, formulation design is crucial for optimizing drug delivery and therapeutic outcomes.
(e) Prediction of Metabolite Structure: These are crucial for understanding how a drug will be processed in the body, identifying potential active or toxic metabolite. Computational simulations provide insights into metabolic pathways and transformations, aiding in the optimization of drug candidate to enhance efficacy and safety. This predictive capability helps in designing drugs with favorable metabolic profiles. Thus, predicting metabolite structures is essential for ensuring safe and effective drug delivery.
(f) Assessment of Drug Transport across Biological Barriers: This prediction helps how drugs will be metabolized, revealing potential active or toxic byproducts. Computational simulations provide insights into these metabolic transformations, enabling the design of drug candidates with improved efficacy and reduced toxicity. This predictive approach ensures that drugs have favorable metabolic profiles, optimizing their safety and therapeutic performance. Thus, predicting metabolite structure is vital for safe and effective drug delivery.

1.2.1.2 Molecular Docking Studies

Molecular docking studies predicts the preferred orientation of drug molecule to the binding site on receptor to form a stable complex. These computational simulations used to predict the binding affinity and interactions between the drug molecule and the target receptor. These contribute to this field by (1) Prediction of Drug-receptor interactions (2) Virtual screening of drug candidates (3) Lead optimization (4) Exploring drug-target binding mechanisms (5) Assessment of drug-induced toxicity (6) Design of drug delivery systems [5, 13, 14].

(a) Prediction of Drug-Receptor Interactions: it is used to identify the optimal binding modes and affinity of drug candidate to their targets. Computational simulations facilitate understanding these interactions at atomic level, guiding the design and optimization of drugs for enhanced efficacy and specificity. This approach aids in selection of the most promising compound for further development. Thus, prediction of drug-receptor interactions is crucial for advancing drug delivery systems.
(b) Virtual Screening of Drug Candidates: It enables the efficient identification of promising compound from large libraries by predicting their binding affinity to biological targets. Computational simulations rank these compounds based on potential interactions, streamlining the drug discovery process. This approach accelerates the identification of high-potential candidates for further experimental validation. Thus, virtual screening of drug candidates is crucial for optimizing drug delivery and expediting the development of effective therapeutics.
(c) Lead Optimization: This is used for refine drug molecule by improving their binding affinity, specificity and pharmacokinetic properties. This process enhances the therapeutic potential and safety profile of the compound. Thus, it is crucial for effective and efficient drug delivery system.
(d) Exploring Drug-Target Binding Mechanisms: They reveal the precise interactions and conformational changes upon binding. This insight helps optimize drug design, for improve efficacy and specificity. Consequently, it enhances the development of effective drug delivery systems by targeting key molecular interactions.
(e) Assessment of Drug-Induced Toxicity: It predicts potential adverse interactions and off-target effects at the molecular level. This approach helps identify and mitigate toxicological risks early in drug development process. Consequently, it enhances the safety and efficacy of drug delivery systems.
(f) Design of Drug Delivery Systems: It enables the precise prediction of drug-target interactions and optimal binding conformations. This approach aids in tailoring delivery mechanisms to enhance drug stability, bioavailability, and therapeutic efficacy. Consequently, it ensures more efficient and targeted drug delivery of drugs within the body.

1.2.1.3 Quantitative Structure-Activity Relationship (QSAR)

QSAR models relates the chemical structure of drug molecule to their therapeutic activity. By analyzing the relationship between the chemical properties of a drug molecule and its biological activity, QSAR models help in predicting the activity of new drug candidates. These models contribute to the field by (1) Prediction of biological activity (2) Optimization of pharmacokinetic properties (3) Identification of structural-activity relationships (SAR) (4) Prediction of drug-drug interactions (5) Design of drug delivery systems (6) Virtual screening and lead optimization [15, 16].

(a) Prediction of biological activity: It leverages statistical correlation between chemical structure and biological effects. This method allows for rapid assessment and optimization drug candidates' safety and efficacy profile. Consequently, it accelerates the development of drug delivery systems by predicting the potential biological activity of new compound.
(b) Optimization of pharmacokinetic properties: It involves predicting and enhancing how drugs are absorbed, distributed, metabolized, and excreted. This approach guides the design of drug candidates with improved bioavailability and reduced side effects. Consequently, it ensures more efficient and effective drug delivery systems by tailoring pharmacokinetic profile.
(c) Identification of structural-activity relationships (SAR): It elucidates how changes in chemical structure influence biological activity. This analysis guides the optimization of drug candidates for enhanced efficacy and specificity. Consequently, it facilitates the development of more effective drug delivery systems by tailoring molecular structures to desired pharmacological outcomes.
(d) Prediction of drug-drug interactions: It predicts potential interactions between different drugs based on their chemical structures. This analysis aids in identifying and mitigating risks of adverse interactions, optimizing drug combinations for enhanced therapeutic outcomes. Consequently, it ensures safer and more effective drug delivery systems by considering potential interactions at molecular level.
(e) Design of drug delivery systems: They facilitate the optimization of delivery mechanisms for improved drug targeting and release kinetics. This approach enhances the understanding how molecular structure influences drug delivery efficiency and bioavailability, guiding the development of tailored delivery systems. Consequently, it enables the drug design of more effective drug delivery strategies through computational simulations at molecular level.
(f) Virtual screening and lead optimization: These enable efficient identification and refinement of promising drug candidates from large libraries based on molecular properties and biological activities. This approach accelerates drug discovery by prioritizing compounds with optimal pharmacological profiles for further development. Consequently, it streamlines the design of effective drug delivery systems through computational simulations at molecular level.

1.2.1.4 Molecular Dynamic (MD) Simulations

These simulations track the movement of atoms and molecules over time. In drug delivery, MD simulations can provide insights into how drug molecules interact with cell membranes, how they taken up by cells, and how they release from drug carriers. MD simulations can also helps in studying the stability of drug formulations and predicting their behavior under different conditions. These simulations contribute to field by (1) Understanding Drug-receptor interactions (2) Exploring drug permeation across barriers (3) Prediction of drug solubility and stability (4) Design of drug delivery systems (5) Prediction of protein-ligand kinetics (6) Assessment of drug induced conformational changes [17, 18].

(a) Understanding Drug-Receptor Interactions: It reveals the dynamic and temporal aspects of binding, including stability and conformational changes. This detailed insight helps optimize drug design for improved efficacy and specificity. Consequently, MD simulations enhance the accuracy of computational drug delivery systems by modeling real-time molecular interactions.
(b) Exploring Drug Permeation across Barriers: It provides detailed insights into how drugs traverse biological membranes. This approach captures the dynamic interactions and pathways of permeation, aiding in the design of drugs with optimal absorption and bioavailability.
(c) Prediction of Drug Solubility and Stability: It helps to understand how drugs behave in different environments. This approach provides insights into solubility profiles and stability under physiological conditions, guiding the formulation for optimal performance.
(d) Design of Drug Delivery Systems: This allows for the detailed analysis of drug encapsulation, release mechanisms, and interactions with drug vehicles. This approach optimizes the formulation and delivery methods to enhance stability, bioavailability, and targeted delivery. Consequently, MD simulations significantly improve the effectiveness of drug delivery systems at the molecular level.
(e) Prediction of Protein-Ligand Kinetics: It provides insights into the binding and unbinding rates of drug molecules to their targets. This approach helps in understanding the duration and stability of drug-target interactions, which is crucial for optimizing drug efficacy and dosing regimens. Consequently, MD simulations enhance the design and drug delivery systems by accurately modeling the kinetics of drug action at molecular level.
(f) Assessment of Drug Induced Conformational Changes: It reveals how drug binding affects the structure of biological target. This approach provides detailed insights into the dynamic alterations and stability of drug-target complexes, crucial for understanding mechanism of action and potential side effects. Consequently, these aid to optimizing drug design and delivery system by capturing the conformational dynamics at the molecular level.

1.2.1.5 Drug Carrier Design

Molecular modeling is also used in the design of drug delivery systems such as nanoparticles, liposomes and micelles. By modeling the interactions between drug molecules and carrier materials, researchers can optimize the design of drug carriers to improve drug delivery efficiency and reduce side effects. These simulations contribute to this field by (1) Optimization of carrier-drug interactions (2) Prediction of carrier physicochemical properties (3) Design of targeted drug delivery systems (4) Assessment of carrier stability and biocompatibility (5) optimization of drug release kinetics (6) Prediction of carrier-cell interactions [19, 20].

(a) Optimization of Carrier-Drug Interactions: It ensures that the drug is efficiently encapsulated, protected, and released at the target site. Computational simulations provide detailed insights into the binding affinity and stability of carrier-drug complexes, guiding the design of carriers for optimal performance. Consequently, this approach enhances the effectiveness and precision of drug delivery systems at the molecular level.
(b) Prediction of Carrier Physicochemical Properties: It ensures that carrier possess optimal solubility, stability, and biocompatibility. Computational simulations provide detailed insights into how these properties influence drug capsulation and release. Consequently, this approach enhances the development of efficient and effective drug delivery systems at the molecular level.
(c) Design of Targeted Drug Delivery Systems: It involves creating carriers that specifically bind to target cells or tissues. Computational simulations optimize the interaction between the drug, carrier, and target, enhancing specificity and efficacy. Consequently, this approach improves the precision and effectiveness of drug delivery at the molecular level.
(d) Assessment of Carrier Stability and Biocompatibility: It ensures safe and effective delivery systems and computational simulations predict interactions between carriers and biological systems, guiding the selection and optimization of materials. Consequently, this approach enhances the development of biocompatible carriers for efficient drug delivery at the molecular level.
(e) Optimization of Drug Release Kinetics: It ensures controlled and targeted release of drugs and computational predict release rates and mechanisms, guiding the design of carriers with desired release profiles. Consequently, this approach enhances the development of efficient drug delivery systems at the molecular level.
(f) Prediction of Carrier-Cell Interactions: It ensures efficient targeting and uptake by specific cells or tissues and computational simulations predict the binding affinity and internalization pathways, guiding the design of carriers for enhanced cellular interactions. Consequently, this approach improves the precision and effectiveness of drug delivery at the molecular level.

Molecular Modeling Software/Tools are depicted in Table 1.1.

Table 1.1 Molecular modeling software/tools

S. No.	Software/tool	Description	Example of drugs
1	GROMACS	Molecular dynamics simulations for biochemical molecules	Simvastatin, doxorubicin, cisplatin, paclitaxel Ibuprofen, Aspirin, Tamoxifen, Lidocaine, Epirubicin, Cyclophosphamide
2	AMBER	Suite of bimolecular Simulation programs including Molecular dynamics and quantum calculations	Doxorubicin, Cisplatin, Paclitaxel, Tamoxifen, Metrexate, Imatinib, Atorvastatin Sildenafil, Docetaxel, Ritonavir
3	NAMD	High-performance molecular dynamics for large Bimolecular systems	Paclitaxel, Doxorubicin, Cisplatin, Docetaxel, Tamoxifen Methotrexate, Ritonavir, Imatinib, Vorinostat, Venetoclax
4	CHARMM	Modeling the structure and Behavior of bimolecular systems	Asiprin, Doxorubicin, Paclitaxel, Tamoxifen, Ibuprofen, Ritonavir, Cisplatin, Atorvastatin, Sildenafil, Imatinib
5	Auto Dock	Automated docking of small molecules to receptor targets	Tamoxifen, Ritonavir, Atorvastatin Sildenafil, Imatinib, Doxorubicin Paclitaxel, Cisplatin, Docetaxel Methotrexate
6	Schrödinger Suite	Comprehensive suite for molecular modeling and drug design	Imatinib, Soldenafil, Atorvastatin Ritonavir, Doxorubicin, Paclitaxel, Tamoxifene, Cisplatin, Methotrexate Docetaxel
7	Gaussian	Computational chemistry software for electronic structure modeling	Ibuprofen, Asiprin, Tamoxifen, Ritonavir Atorvastatin, Sildenafil, Doxorubicin Cisplatin, Paclitaxel, Imatinib
8	VMD	Visualization and analysis of molecular dynamics simulations	Insulin, Doxorubicin, Paclitaxel Tamoxifen, Cisplatin, Atorvastatin, Ritonavir, Imatinib, Methotrexate Docetaxel
9	LIGPLOT	Generates schematic diagrams of protein–ligand interactions	Ritonavir, Tamoxifen, Atorvastatin, Sildenafil, Imatinib, Doxorubicin Paclitaxel, Cisplatin, Docetaxel, Methotrexate
10	OpenMM	High performance toolkit for molecular simulations	Vancomycin, Doxorubicin, Paclitaxel Tamoxifen, Cisplatin, Atorvastatin Ritonavir, Imatinib, Methotrexate Docetaxel

1.2.2 Molecular Docking Studies

These simulations are helpful to predict drug molecule interaction with binding site and help to determine the optimal binding orientation and affinity of the drug molecule, guiding the design of molecules with improved efficacy and selectivity. By simulating these interactions researcher can identify potential drug candidates and

refine their structure to enhance binding properties. Ultimately, molecular docking aids in understanding the molecular mechanisms of drug action and optimizing drug delivery systems for better therapeutic outcomes. These are a very important components in computational simulations in drug delivery at the molecular level and fit into process by (1) Target identification (2) Molecular modeling (3) Docking algorithm (4) Scoring and analysis (5) Validation (6) Lead optimization [21, 22].

1.2.2.1 Target Identification

These simulations identify the biological molecule that interacts with the drug molecule. Accurate identification of these targets enables to predict site and mechanism of drug binding with receptor i.e. biological molecule. This helps in designing of drug with high specificity and efficacy, reducing off-target effects. Ultimately, effective target identification enhances overall success of drug delivery system by ensuring that therapeutic agents precisely modulate intended biological pathways. The target identification contributed in this field by (1) Selection of receptor protein (2) Understanding molecular mechanisms (3) Prediction of binding sites (4) Validation of drug target interactions (5) Identification of off-target interactions [23–25].

(a) Selection of Receptor Protein: It determines the specific biological targets for drug interaction and this process involves selecting receptors relevant to the therapeutic mechanism, guiding simulations to predict drug-receptor interactions accurately. Consequently, it aids in designing tailored drug delivery systems for optimal therapeutic outcomes at the molecular level.
(b) Understanding Molecular Mechanisms: It elucidates the underlying biological pathways and interactions crucial for drug action. This knowledge informs the selection of relevant targets and guides simulations to accurately drug-receptor interactions. Consequently, it facilitates the design of targeted drug delivery systems, optimizing therapeutic outcomes by precisely modulating molecular at the cellular level.
(c) Prediction of Binding Sites: It enables the precise determination of where drugs interact with biological targets. This information guides the selection of relevant targets and helps in simulating drug-receptor interactions accurately. Consequently, it facilitates the design of targeted drug delivery systems, optimizing therapeutic outcomes by effectively targeting specific molecular sites at the cellular level.
(d) Validation of Drug Target Interactions: It ensures the accuracy and reliability of predicted interactions and this process involves comparing simulation results with experimental data to confirm the efficacy of selected targets. Consequently, it enhances the design of targeted drug delivery systems by providing confidence in the predicted drug-receptor interactions, ultimately optimizing therapeutic outcomes at the molecular level.
(e) Identification of Off-Target Interactions: It helps anticipate potential unintended effects of drugs. By analyzing the interactions between drugs and various bio-

logical molecules, it provides insights into off-target binding sites and potential side effects. Consequently, it enables the design of targeted drug delivery system that minimizes off-target interactions, optimizing therapeutic efficacy and safety at the molecular level.

1.2.2.2 Molecular Modeling

These are integral to docking studies within computational simulations of drug delivery and are used to predict 3D structure of binding site and drug molecule. It contributes in the field by (1) Structure preparation (2) Ligand conformational sampling (3) Receptor flexibility (4) Scoring function development (5) Validation and interpretation (6) Lead optimization [26, 27].

(a) Structure Preparation: These studies involve optimizing geometry and energetics of bimolecular structures prior to simulations. This ensures accurate representation of drug-target interactions, aiding in the prediction of binding modes and affinities. Consequently, it enhances the design of drug delivery systems by providing reliable insights into molecular interactions at the atomic level.
(b) Ligand Conformational Sampling: These studies explore various conformations of drug molecules to predict their interactions with target proteins accurately. This process allows for the identification of favorable binding modes and optimization of drug-receptor interactions. Consequently, it enhances the design of drug delivery systems by providing insights into the most stable and effective ligand conformations at molecular level.
(c) Receptor Flexibility: This study accommodates the dynamic nature of target proteins, ensuring accurate prediction of drug-target interactions. This process considers conformational changes in the receptor upon ligand binding, enhancing the reliability of docking simulations. Consequently, it aids in the design of the drug delivery of molecular interactions at the atomic level.
(d) Scoring Function Development: These studies refine algorithms to assess the strength of ligand-receptor interactions accurately. This process improves the prediction of binding affinities, guiding the selection of potential drug candidates for further development. Consequently, it enhances the design of drug delivery systems by providing reliable metrics to evaluate molecular interactions at the atomic levels.
(e) Validation and Interpretation: These studies validates the simulation results against experimental data and interpret the significance of predicted interactions. This process ensures the reliability of computational predictions and guides the selection of promising drug candidate for further investigation. Consequently, it enhances the design of drug delivery system by providing confidence in the predicted molecular interactions at the atomic level.
(f) Lead Optimization: These studies involve refining initial drug candidates to enhance binding affinity and specificity. This iterative process utilizes computational simulations to optimize molecular structures for improved drug-target

interactions. Consequently, it facilitates the design of drug delivery systems by identifying promising leads for further development at the molecular level.

1.2.2.3 Docking Algorithm

These simulations predict the optimal binding orientation and affinity of drug molecule with its binding site on the receptor and facilitate high-throughput virtual screening, identifying promising drug candidates efficiently. Ultimately, they enhance the drug design by predicting interactions that optimize therapeutic efficacy and specificity. These contribute to the field by (1) Prediction of ligand-receptor modes (2) Scoring of ligand binding affinities (3) Accounting for receptor flexibility (4) Virtual screening of compound libraries (5) Lead optimization and design (6) Analysis of binding interactions [26, 27].

(a) Prediction of Ligand-Receptor Modes: These studies determine how ligands interact with target proteins at the molecular levels and this process identifies the most favorable binding conformations and interaction sites, guiding the design and optimization of drug candidates. Consequently, it enhances drug delivery systems by accurately modeling and predicting effective drug-target interactions.
(b) Scoring of Ligand Binding Affinities: These studies evaluate the strength and ability of drug-receptor interactions in molecular docking studies. This process ranks potential drug candidate based on predicted binding energies, guiding the selection of the most promising compounds. Consequently, it enhances the design of drug delivery systems by prioritizing ligand with optimal binding characteristics for further development.
(c) Accounting for Receptor Flexibility: These studies incorporate the dynamic movements and conformational changes of target proteins during molecular docking studies. This approach improves the accuracy of predicting ligand binding by considering the receptor's adaptability upon ligand interaction. Consequently, it enhances the design of drug delivery system by providing more reliable simulations of drug-target interactions at molecular level.
(d) Virtual Screening of Compound Libraries: These studies rapidly evaluate numerous potential drug candidates against target proteins. This process identifies the most promising compound based on predicted binding affinities and interactions. Consequently, it accelerates drug discovery and enhances the design of drug delivery systems by efficiently pinpointing viable drug candidates for further development.
(e) Lead Optimization and Design: These b studies refine drug candidates to improve their binding affinity, specificity, and pharmacokinetic properties. This process iteratively adjusts molecular structures based on computational predictions to enhance drug efficacy. Consequently, it enhances drug delivery systems by developing optimized leads that are more effective and targeted at molecular levels.

(f) Analysis of Binding Interactions: These studies examine how drug molecules interact with target proteins at the molecular level. This process identifies key binding sites, interaction types, and energetics, providing detailed insights into drug-receptor compatibility. Consequently, it enhances drug delivery systems by guiding the design of molecules with optimal binding characteristics and therapeutic efficacy.

1.2.2.4 Scoring and Analysis

This is very essential for identifying and refining drug molecular structure. Scoring function evaluates the binding affinity between drug molecule and binding site of a receptor and quantifying the interactions. This scoring helps prioritize potential drug candidate by predicting their efficacy and stability. Subsequent analysis of these scores provides insights into the molecular mechanisms of binding, guiding the optimization of drug molecular structure for enhanced therapeutic action. Scoring and analysis contributes to this field by (1) Scoring of ligand-receptor interactions (2) Analysis of binding interactions (3) Validation of docking results (4) Lead optimization and SAR Analysis (5) Prediction of ADMET properties (6) Design of drug delivery system [28, 29].

(a) Scoring of Ligand-Receptor Interactions: These studies quantify the strength and stability of the binding between a drug and its target protein. This evaluation ranks potential drug candidate based on predicted binding affinities, helping identify the most promising compounds. Consequently, it enhances drug delivery systems by prioritizing ligand with optimal interaction profiles for further development and testing.
(b) Analysis of Binding Interactions: These studies examine the detailed interactions between a ligand and its receptor, such as hydrogen bonds, hydrophobic contacts, and Van der Waals forces. This evaluation helps understand the molecular basis of binding affinity and specificity. Consequently, it enhances the drug delivery system by informing the design and optimization of compounds with favorable binding characteristics.
(c) Validation of Docking Results: These studies involve comparing computational predictions with experimental data to ensure accuracy and reliability. This process verifies the predicted binding modes and affinities, confirming the validity of the docking simulations. Consequently, it enhances drug delivery systems by providing confidence in the identified drug candidates and their interactions at molecular level.
(d) Lead Optimization and SAR Analysis: These studies refine drug candidate to improve their efficacy and binding properties. This process involves iterative adjustments to molecular structures based on docking scores and interaction pattern, enhancing the drug's activity. Consequently, it improves drug delivery systems by developing optimized leads with enhanced therapeutic potential and specific target interactions.