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Computational modeling for formulation design

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Formulation design is an important phase in the drug development process. However, this process at an experimental level requires exhaustive experimental work. Excipient selection, prediction of solubility, encapsulation efficiency, release patterns, drug absorption, stability, and mechanism of nanoparticle formation are some of the essential steps in formulation design. The use of various computational tools, including quantitative structure–activity relationships (QSARs), molecular modeling, molecular mechanics, discrete element modeling, finite element method, computational fluid dynamics, and physiologically based pharmacokinetics (PBPK) modeling, help in the identification of drug product inadequacies and to recommend avenues for understanding complex formulation design in less time with lower investment. Here, we focus on computational modeling tools used in formulation design and its applications.

Introduction

Pharmaceutical formulation design is an important process in drug discovery, wherein the drug is combined with different excipients to form a drug formulation to improve the solubility, efficacy, and stability of the drug. The physical and chemical properties of drugs are vital parameters for the selection of appropriate excipients to achieve the desired formulation properties. The performance and properties of the drug formulation also depend on the formulation type. The trial-and error-method is the most appropriate technique to predict the suitable excipient for the development of drug formulations. Nevertheless, the process is time-consuming and expensive [1,2].

In pharmaceutical research, several computational tools are used to design, develop, and streamline drug discovery, collectively forming the basis of computer-aided drug designing. These also have an important role in solving the problems frequently encountered during pharmaceutical formulation design, including stability, solubility, tensile strength, porosity, dissolution, and *in vivo* performance [3]. Quantitative mechanistic models aid the prediction of the composition of a formulation with desired properties and also help to reduce the material expenses incurred during experimental formulation design trials [4,5]. The prediction and quantification of nano- and microscale molecular interactions, microscale cellular mechanisms, and macroscopic physiological effects in the uptake, targeting, and delivery of the drug on multiple scales are important parameters in the design of drug delivery systems. Recently, the US Food and Drug Administration (FDA) exploited the use of computational tools in the design of various medical devices, which could help identify and correct problems during the formulation stage before the drug reaches the market [6]. Therefore, computational modeling along with experimental work can be used to model various formulation properties [1,4,7]. The computational tools used in formulation design are detailed in Table 1 [8–24], whereas Table 2 details the various software used for QSAR and quantitative structure–property relationship (QSPR) model generation.

Applications of computational modeling in formulation design

Computational tools are widely used in formulation design by providing mechanistic insight into the interactions between dif-

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TABLE 1

Examples of computational tools used in formulation design

Computational tool	Description	Example applications	Refs
Quantitative structure–activity relationship (QSAR)	Physical and chemical properties of molecules are correlated with biological activities	In the drug discovery and design process, distinguishing drug-like molecules from nondrug-like molecules, prediction of biological, physicochemical, and PK properties, drug resistance, and toxicity prediction	[8,9]
Quantitative structure–property relationship (QSPR)	Mathematical correlation between the descriptor properties (e.g., LogP, pKa, etc.) of the drug molecule structure with the property under investigation	Screening and selection of effective drug candidates for novel drug delivery systems Prediction of formulation composition, including polymer blends and surfactant:cosurfactant ratio	[5,10]
Molecular dynamics (MD)	Provides a view of the dynamic evolution of a system wherein atoms and molecules interact for a fixed period	Interpreting physical basis of structure and function of biological macromolecules Investigation of the structure and complex, protein folding, molecular recognition, conformational changes, ion transport in biological systems, and protein stability Rational design and development of nanocarriers and selection of compatible excipients	[11–14]
Molecular modeling	Includes quantum mechanics (QM) and molecular mechanics (MM) QM uses electrons in the calculation to derive properties depending upon the electronic distribution MM uses classical mechanics (Newtonian Mechanics) to describe physical basis behind models; relies on force fields with embedded empirical parameters	Studying reaction pathways, prediction of properties for catalysts that have not been synthesized; generates valuable information for a given system from various experimental techniques	[15–17]
Finite element method (FEM)	Computational numerical technique helpful in modeling physical phenomena	Compaction modeling of pharmaceutical powders during tablet compression Determination of mechanism of mass flow by tracking movement of powder rather than single particles between different simulated environment areas	[18,19]
Discrete element modeling (DEM)	Provides better insight into flow dynamics of particles by modeling moving boundaries	Understanding particle–particle and particle–environment interactions during pharmaceutically relevant processing Modeling of blending, granulation, milling, die-filling, compression, coating as well as material storage and transport	[20]
Computational fluid dynamics (CFD)	Solving equations that govern fluid flow by using numerical methods	Simulation of unit operations involving dynamics of mixing, dead zone identification, and shear rate distribution	[21]
Physiologically based pharmacokinetics models (PBPK)	Integrates physiology and anatomical parameters of animals or humans, physicochemical properties of drugs, and the final formulation to predict absorption, distribution, metabolism, and excretion (ADME) of a drug *in vivo*; aids QbD implementation in drug development	Developing *in silico* models to simulate drug absorption, assess performance and feasibility of ER formulations, thereby reducing need for multiple *in vivo* studies	[22–24]

ferent constituents and predicting the behavior of drugs during the formulation process. They also aid the selection of excipients, in the conduction of preliminary studies, in the design of various formulations, including tablets, nanoparticles, liposomes, and topical formulations, as well as in the prediction of toxicity, stability, and *in vivo* performance of formulation. Examples of applications of these tools in formulation design are discussed here.

Selection of excipients

QSPR models were developed by correlating theoretically predicted physicochemical polymeric properties with formulation properties

TABLE 2

Software available for QSAR and QSPR model generation

Computational tools	Examples of available software	Further information
QSAR and QSPR	VEGA Platform, DEMETRA, OCHEM, AMBIT, ADMEWORKS ModuleBuilder, TerraQSAR, Simulation Plus, QSAR and Modeling Society, Chemoinformatics, DRAGON, Molconn-Z, MODEL, etc.	http://vega.marionegri.it/wordpress/resources/qsar-in-silico-tools

by using the Vlife MDS 4.2 builder module. Such models are useful in determining formulation compositions, such as the polymer blend, and for investigating the mechanism of drug release and, thus, drug bioavailability, which could facilitate the development of new formulations or optimization of existing ones [7].

Tableting process

Given that the particulate system forms the core of formulation development in any pharmaceutical company, it is important to understand the macroscopic behavior that occurs during the processing of solid dosage forms. Such information will aid the design of relevant equipment, improve the efficiency of the process and its scale-up. Various computational modeling tools, including computational fluid dynamics (CFD), finite element method (FEM), and discrete element modeling (DEM), have been used to gain detailed insights into these processes [20].

Process modeling (CFD, FEM, and DEM) in formulation design

DEM was used to study the impact of flow properties of powder on die-filling and tablet compression processes. As the cohesiveness between the particles increased, the time taken to fill the die also increased. These results were in accordance with experimental data that showed that the weight variability between tablets for cohesive powders decreased at a lower tableting speed [25]. A combination of DEM with CFD was used to simulate the die-filling process under the influence of both air and vacuum. The mass flow rate increased as the density and particle size increased in the case of small, light particles, whereas a minor effect was observed for coarse, dense particles in air-inert regions. Under vacuum, the mass flow rate was unaffected [26]. DEM has also been used to study the packing of materials. The results of coordination number and porosity obtained via simulation suggested that DEM can be used for the structural analysis of particle packing [27]. FEM coupled with DEM was used to study the behavior of individual granules and the granule bed under compression in simulation studies. This method can also be used to study the densification and deformation behavior of granules individually, which provides detailed insights into the processes occurring during granular material compression [28].

The effect of various factors on mixing and their influence on the tablet-coating process in a pan coater was studied computationally by using a DEM model. A slower axial dispersion was observed on horizontal rotation of the mixer, whereas a higher optimal tilt angle was found to enhance axial mixing. However, the fill level and rotation speed of the coating pan were found to have negligible effects on mixing rate. These results were experimentally validated, thus strengthening the use of simulation tools in this instance [29].

Predictive modeling of extended release formulation

CFD coupled with the finite element volume method was used for the prediction of metformin release from a hydroxypropyl methyl cellulose extended-release formulation. The CFD model developed was used to evaluate the effect of tablet geometry (tooling shape and size) on the dissolution profile. In addition, a PBPK model developed using GastroPlus™ software to predict the in vivo performance of a new high-dose tablet (1000 mg) compared with the currently available low-dose (2 × 500 mg) marketed tablet showed similar in vivo exposure. The results of bioequivalence studies of the high-dose tablet complimented the simulation results obtained. Thus, the developed model could accelerate the product development process in this instance [30].

The carbamazepine (CBZ) PK was determined following the oral administration of four marketed formulations under fasted and fed conditions [i.e., immediate-release (IR) suspension and tablet, extended-release (XR) tablet and capsule]. The PK data after oral administration of the IR formulation was collected from the literature and fit into a suitable model, which was further validated for the PK profiles of other IR formulations. This validated model was used for the PK prediction of XR formulations, including the identification of optimum dissolution conditions for such formulations and critical formulation variables that showed a PK shift. The simulations also allowed the incorporation of intersubject variability as a parameter affecting PK. The results indicated that the validated models can be used in prediction and formulation optimization during the quality by design (QbD) approach [31].

Physiologically based pharmacokinetic modeling for formulation design

Numerous studies are available wherein PBPK modeling has been successfully used for the prediction of the *in vivo* performance of drugs. *In vivo* plasma profiles of three Biopharmaceutical Classification System class II compounds in a fasted state were predicted using GastroPlus™ software. Factors, such as permeability, solubility data in Fasted state simulated intestinal fluid (FaSSIF), ionization, lipophilicity, *in vitro* metabolism, and PK data, were considered in the model development. The results fit well with experimental observations, which showed a good correlation when FaSSIF rather than aqueous media was used for solubility studies [32]. PBPK modeling can be coupled with biorelevant dissolution test data to obtain a more precise picture of the *in vivo* performance of a drug and its dosage form, and the impact of various factors affecting these [22]. Biorelevant dissolution testing along with PBPK modeling was used to study the effect of pre-absorptive (disintegration and dissolution), absorptive (drug absorption and efflux) and postabsorptive (drug distribution and clearance) factors affecting the oral bioavailability of atazanavir (ATZ). The plasma profile obtained via simulation studies revealed that the ATZ oral bioavailability was sensitive to the volume of distribution rather than to pre-absorptive and absorptive factors [23].

Solubility prediction in the presence of additives

Complexation is a generally used method to enhance the solubility of drugs. The effects of the presence and absence of an auxiliary agent, L-arginine (L-Arg) on the complexation efficiency of etodolac (ETD) with hydroxypropyl-β-cyclodextrin (HP-β-CD) in terms of the aqueous solubility and dissolution properties were examined using the Maestro module (version 10.7, Schrödinger). Prime MM-GBSA module (version 4.5, Schrödinger) was used to obtain the binding affinity (ΔG), which helps to determine stability of the binary and ternary inclusion complexes. The S isomer of ETD had higher binding affinity than the R isomer for both the binary and ternary inclusion complexes (Table 3). L-Arg formed a bridge between HP-β-CD and ETD via electrostatic and hydrogen bond interactions, thus enhancing the stability of the complex. Molecular dynamics (MD) simulations demonstrated that L-Arg was located on the outer surface of the complex and enhanced the complex polar surface, which led to an increase in the solubility of

TABLE 3

Binding affinity values of ETD isomers

ETD isomer	Binding affinity value		Refs
	Binary inclusion complex	Ternary inclusion complex	
S	−37.128 kcal/mol	−51.464 kcal/mol	[33]
R	−27.326 kcal/mol	−43.061 kcal/mol	

the inclusion complex. Figure 1 shows the hydrophobic and hydrophilic surface area of ETD, and the binary and ternary inclusion complexes [33]. A similar study was carried out to increase the solubility of efavirenz (EFV) by complexing with HP-β-CD using L-Arg. Figure 2 shows the top and side view of the binding pose of the EFV supramolecular ternary complex predicted by docking [34]. A study using ciprofloxacin (CIP) complexed with mono-6-deoxy-6-aminoethyl amino-β-cyclodextrin (Et-β-CD) showed that this complex improved the solubility of CIP as a result of the superior complexation of CIP and Et-β-CD to the oval shape of the secondary rim of Et-β-CD [35].

Molecular modeling-based quantum mechanics (QM) calculations performed using Gaussian09 software aid the determination of intermolecular interactions and the binding energy, whereby it was observed that the higher the binding energy, the more stable the intermolecular drug–polymer interaction and, thus, the better the drug–polymer miscibility. Based on these theoretical approaches, solubility parameter calculations indicate that compounds with similar Hansen solubility parameter (δ) values are said to be miscible and vice versa [36]. The miscibility of indomethacin (IND) in different carriers, such as polyethylene oxide (PEO), glucose (GLU), and sucrose (SUC), was predicted by developing computational models. Compounds with $\Delta\delta$ <7.0 MPa0.5 and $\Delta\delta$ >10.0 MPa0.5 indicated the miscibility and immiscibility of the system, respectively. Thus, the smaller $\Delta\delta$ values ($\Delta\delta$ <2.0 MPa0.5) of IND/PEO indicated that the miscibility was the result of van der Waals forces (δvdW), whereas the greater $\Delta\delta$ values of IND/SUC or IND/GLU indicated intermediate miscibility and immiscibility because of the prevalence of electrostatic forces, respectively. Thus, molecular-level insight into intermolecular interactions and the fundamental mechanisms using a MD approach aids the robust and rational development of amorphously dispersed molecules [12].

Self-nanoemulsifying drug delivery systems (SNEDDS) were developed using stearyl amine (SA) to increase the solubility and dissolution of meloxicam (MLX). The role of SA and the interaction between SA and MLX were examined by MD simulations in the lipid environment (i.e., Labrafil M). The differences in the pKa, the physiological charge of both molecules, and the ionic complexation-type interaction between SA and MLX were the

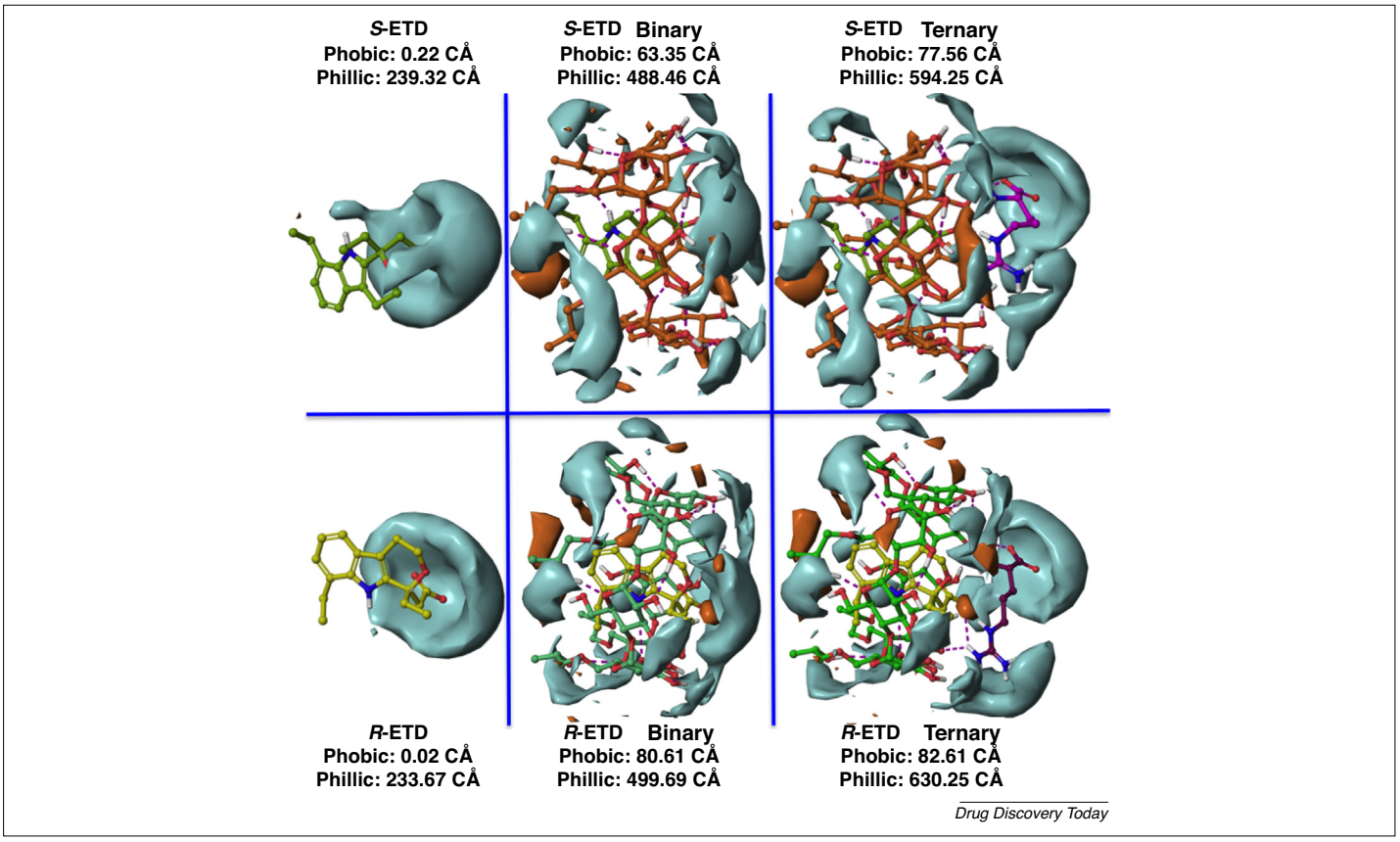

FIGURE 1

The complexation efficiency of etodolac (ETD) in both S and R configuration with hydroxypropyl-β-cyclodextrin (HP-β-CD) was examined in the presence and absence of L-arginine (L-Arg). The figure shows the hydrophobic (brown) and hydrophilic (blue) surface area of ETD, the binary complex, and ternary inclusion complexes [33]. Abbreviation: CÅ, cubic Angstroms.

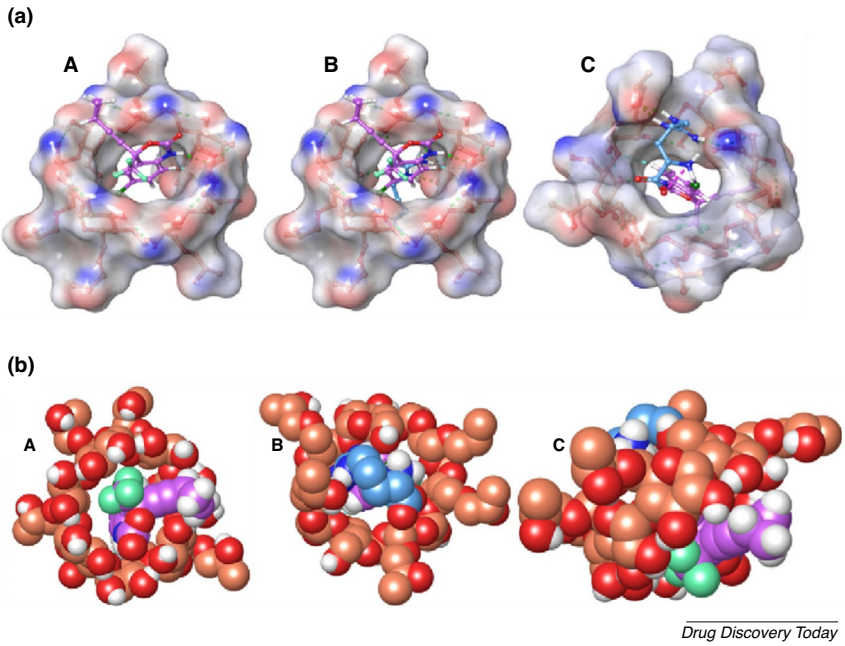

FIGURE 2

The binding pose of the efavirenz (EFV) supramolecular ternary inclusion complex predicted by docking. (a) Top and (b) (b) side view of the EFV supramolecular ternary complex. The color coding is as follows: brown, hydroxypropyl-β-cyclodextrin (HP-β-CD); purple, EFV; blue, L-arginine (L-Arg). The electrostatic region in (a) includes electronegative region (red), electropositive region (blue), and hydrophobic regions (gray) [34].

main parameters for solubility enhancement in the presence of SA. The interactions between MLX and SA were found to enhance the solubility in liquid lipid (Labrafil M) [37].

Prediction of drug loading and encapsulation efficiency

QSPR models were built to study the drug-loading capacity of polymeric micelles by understanding the relationship between the polymer structure and the efficacy of micelles as a drug carrier. The QSAR module was used to compute and choose the most appropriate descriptors using the genetic function approximation (GFA) algorithm, which predicts the drug-loading capacity of polymeric micelles. Experimental data confirmed that the relationship between drug-loading ability and microstructure could be simulated, which indicates that selected models are suitable for the quantitative estimation of the drug-loading ability of polymeric micelles [38]. The interaction of the drug with solid lipid nanoparticles and PLGA nanoparticles was modeled using MD simulation and the binding energy was predicted using molecular docking to correlate the entrapment efficiency [39].

Modeling for topical preparations

Predictive mathematical models were developed by using various polycyclic aromatic hydrocarbons, organophosphorus insecticides, and phenoxycarboxylic herbicides to establish a correlation between *in vitro* percutaneous absorption data and physicochemical properties of chemicals. The experimentally predicted values of the permeability coefficient (Kp) and lag time were correlated with log octanol/water partition coefficient (logKo/w) values. This indicated highly significant fit in contrast to independent variables, such as molecular weight (MW) and vapor pressure, which were not significant in improving the prediction of the same values [40,41]. Kp was predicted by developing QSPR models (ChemSite Pro version 5.4) of nonsteroidal anti-inflammatory drugs (NSAIDs) for transdermal delivery. Kp for the transdermal delivery of NSAIDs with clogP or logKo/w values <2 with R^2>0.90 was found to improve with the solubility parameter (δ). Thus, δ has a crucial role in predicting the skin permeability of NSAIDs for transdermal delivery [41,42]. The health hazards caused by exposure of skin to dangerous chemicals were determined by checking the Kp of the chemical in the stratum corneum of human or animal cadaver skin. The various chemical substances with recognized permeability coefficients were used to develop QSAR models that were suitable for the prediction of Kp and physicochemical properties involved in the transdermal transport of the chemicals. Four-descriptor multiple linear regression models were used to fit the observed Kp data with a mean percentage error of 18.8% and regression of 0.828, which indicated that the generated QSAR can be used as an alternative tool for the characterization of dermal hazard and permeability coefficient information [41,43]. The effect of terpenoids and terpenes on the *in vitro* permeability coefficients of haloperidol was also evaluated by QSAR models. This study revealed that permeation enhancer properties, such as specific functional group, level of hydrophobicity, and chemical type, are superior for drug permeation through the skin, which could be helpful in the initial screening and designing of new enhancers. Hence, establishing QSAR relationships was helpful in forecasting the human skin penetration effect of terpenoids and terpene compounds with physicochemical properties similar to haloperidol without the need to conduct experimental trials [41,44].

In situ gel preparation

MD simulations using computer-aided formulation design (Schrödinger tools) were performed to study the function of each ingredient and gelation process (sol to gel transformation) occurring in the nanoemulgel formation of quercetin (Fig. 3). The difference in the physical properties of the systems along with an increase in the interaction between different components at two different temperatures, 275 K (1.85 °C) and 313 K (39.85 °C), which were observed at molecular level, suggests a plausible explanation for the transformation of the formulation from sol to gel phase at 313 K. Different parameters, such as density, number of hydrogen bonds between the formulation and solvent, diffusion coefficients of the solvent and formulation components, and radius of gyration of poloxamer-407 molecules, were used to study the physical properties of the formulation. The results could help in understanding the mechanistic physiological behavior of the dosage form [45].

Formation of nanoparticles

The mechanism of formation of a methotrexate (MTX) nanosuspension based on acid-base neutralization was examined computationally based on structural and electronic properties for isolated MTX molecules and molecular clusters. Quantum chemistry and molecular frontier orbital calculations have a vital role in the reorganization of the reactivity and transport properties of molecules by estimating the acceptors or donors of the electron region of molecules. The computational results suggested that the higher energies of interaction between MTX molecules lead to aggregation in the cationic and zwitterionic states of clusters and vice versa [46]. Dendrimeric nanovectors are the most widely used carriers for biomedical and pharmaceutical applications among the various nanoparticle drug delivery systems available, but understanding the mechanism of drug encapsulation inside the dendrimer cavity and the release of the drug from the drug–dendrimer complex is challenging. The use of computational tools, such as coarse-grained simulation with quantum chemical calculations, can complement experimental methods to determine drug–dendrimer interactions, drug encapsulation inside the dendrimer cavity, and the drug release mechanism from the drug–dendrimer complex by considering various properties, including physicochemical properties of the dendrimer and drug, length of a simulation run, force fields, and so on [47].

The effect of surface chemistry on nanoparticle internalization into cells was studied using computational software, such as LAMMPS, Packmol, and GROMACS 4. The effects of charge density, ligand length, and hydrophobicity were estimated by performing coarse-grained MD simulations of the lipid bilayer interacting with gold nanoparticles, which showed that low charge densities and short-length ligands efficiently and/or successfully penetrate the cell membrane. Thus, it indicates that the penetration of nanoparticles through the cell membrane depends on the surface chemistry of the nanoparticles, the ligand length, and the charge density of the nanoparticles. Predictive tools also help in nanomaterial evaluation before experimentation, thereby increasing the rate of success *in vivo* [13,48,49].

Liposome preparation

The complementary use of computational studies along with experimental studies developed key mechanistic insight for the rational design of liposomal drug delivery systems (LDS). The first simulation of liposomes was performed by Noguchi and Takasu using a Brownian dynamics model, which showed that very small liposomes were formed during the early stages of the process, whereas MARTINI coarse-grain, implicit solvent models and dissipative particle dynamics models were used for larger liposomal system simulations. The authors conducted coarse-grained simulations to identify the hypericin (drug) distribution within the LDS and potential mean force (PMF) for transporting hypericin from the aqueous core to the favored location through the membrane and out of the liposome, respectively. Therefore, this methodology was found to be an essential tool for developing the liposomal membrane properties and the properties that enable drugs to be released from the LDS [50]. QSPR models link the physical, chemical, and structural drug properties and experimental conditions with the remote loading efficiency of drugs into liposomes. The

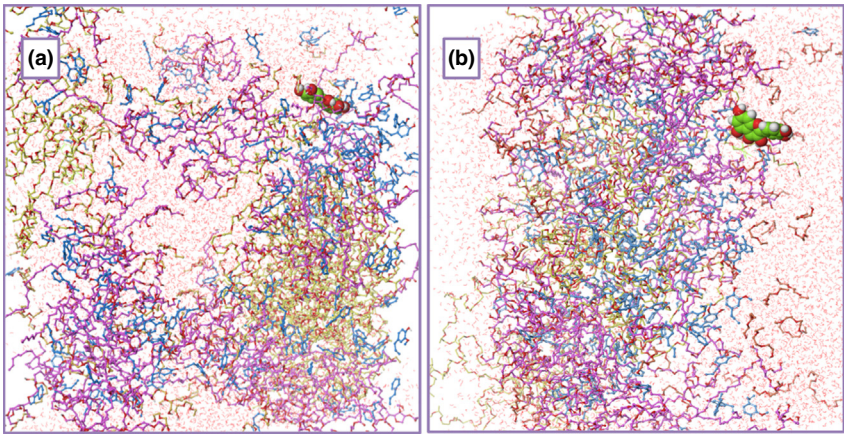

FIGURE 3

Formation of gel inside water during the nanoemulgel formation of quercetin. The formulation components at 275 K (a) and at 313 K (b) are shown. Quercetin is represented in the form of a CPK model in green, whereas cinnamon oil is cyan, Carbitol® is pink, tween 80 is brown, and poloxamer 407 is a yellow ball and tube [45].

development of continuous models (predict the high loading competence) and binary classification models (predict high or low loading effectiveness) were developed and can be used to filter drug databases to identify suitable candidates. Three molecules [two true positives (mupirocin and pravastatin) and one true negative (piroxicam)] were chosen for experimental testing based on experimental considerations and a QSPR model prediction, which indicated that true positives showed a high loading efficiency whereas the true negative revealed medium loading efficiency. Therefore, QSPR modeling can be helpful for the selection of a suitable drug for liposomal formulations and in the development of novel drug delivery systems [10].

Stability of formulations

Physical instability of the amorphous form limits the development of amorphous solid dispersions (ASDs) as well as its long-term stability. The development of molecular descriptors for QSAR modeling applications could be helpful in recommending the best excipients for amorphous state physical stability prediction. Continuous advances in computational modeling applications are valuable for the prediction of ASD development and its solubility and stability, as well as to examine the microscopic interactions of a system by considering the complexities involved in ASD [51]. The complexation of polymers to peptide drugs prevents their chemical degradation, but the stabilization mechanisms involved were unknown, which makes it difficult to prepare specific polymers. The mechanism of the peptide stabilization effect of polyvinyl pyrrolidone (PVP) on the AcVYGNGA peptide was examined using the molecular simulations. The properties of PVP were established using the concomitant use of MD simulation and experimental approaches and correlated with the polymer structure, which is essential for predictive model development. The problems associated with polymer design could be solved by implanting predictive models within an optimization framework. Structure–property relationships can be predicted using MD simulations that can form the basis for designing novel polymers for the stabilization of peptide drugs [52]. Different QM methods were used by Djemil et al. to study the interactions between dopamine, epinephrine, and the β-CD molecule. The authors observed that dopamine formed a more stable complex than did epinephrine with β-CD owing to intermolecular hydrogen bonds [53].

Toxicity prediction

Utilization of computational modeling for the prediction of toxicity of chemicals avoids the failure of molecules during initial phases of the drug discovery process. SARs and resulting algorithms related to toxicity can be developed using the experimental properties of known compounds. Metabolism site and metabolite prediction are significant factors that need to be determined for environmental and commercial chemicals. Computational toxicity models could help not only to enhance the effectiveness of molecular screening by diminishing use of animal studies in drug delivery, ultimately replacing them, but also in repurposing of Food Drug and Administration (FDA)-approved drugs with an improved adverse effect profiles [54].

Concluding remarks

The combined use of experimental studies with various computational approaches, such as QSAR, QSPR, molecular modeling, MD simulation, DEM, FEM, CFD, and PBPK, aids in various stages of formulation development, including the selection of lead excipients, determination of solubility parameters, intermolecular energy contributions, and prediction of drug-release profiles. Utilization of computational modeling in formulation development is still in its nascent stages and, in future, this field can be expected to become an integral part of formulation development, particularly because it can be used to predict factors influencing the design of a dosage form in a hypothetical manner, which is difficult to do in laboratory experiments. Thus, this approach is likely to expedite both the drug development and regulatory processes.

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