Chapter 18

Computer-aided biopharmaceutical model development

Balakumar Chandrasekaran[1], Mohammad F. Bayan[1], Nadia Mansour[1], Rahaf Oweis[1], Raneem Al-Halabi[1], Kumarappan Chidambaram[2] and Rajwinder Kaur[3]

[1]Faculty of Pharmacy, Philadelphia University, Amman, Jordan, [2]Department of Pharmacology, College of Pharmacy, King Khalid University, Abha, Saudi Arabia, [3]Chitkara College of Pharmacy, Chitkara University, Rajpura, Punjab, India

18.1 Introduction

Biopharmaceutical is known as any medical drug that is extracted or semisynthesized from a natural biological source [1]. The process of extraction, evaluation, and development of such pharmaceutical products can be very expensive and time-consuming. In our current generation, we always search for a quick solution. It is the same in the pharmaceutical industry; we should have a quick process and accurate results without disrupting safety or effectiveness. In order to achieve this, researchers decided to use computational models to help them save time and reduce the costs of long production processes [2]. They do not have to wait for in vivo results or data based on actual trials on human beings; these models, such as the quantitative structure-activity relationship (QSAR), allow the prediction of the human response to a specific substance [3].

In the pharmaceutical industry, the safety of any product is regulated by the Food and Drug Administration (FDA) or the European Medicines Agency (EMA). To ensure the quality of a product, the International Conference of Harmonization (ICH) has established some guidelines which have to be considered during the process lifecycle. The process lifecycle includes the following: process development, scale-up and continuous optimization until product discontinuation. According to the International Conference of Harmonisation (ICH) Q8(R2) guidelines, the quality by design (QbD) method is one way of designing an adequate production procedure [4].

Quality by design (QbD) is explained as a method to ensure the quality of products with an understanding and control of the process, along with knowledge of the risks that are entangled in manufacturing procedures. The FDA recently launched the KASA (Knowledge-aided Assessment and Structured Application) system, which performs computer-aided analysis to evaluate the drug products based on their data, manufacturing procedures, and facilities. Although computational pharmaceutics has made considerable improvements in the last few decades, the research and development processes are still based on the time-consuming and expensive traditional trial-and-error experiments. The conventional techniques go through preformulation, formulation optimization, scaling up, and in vivo studies. If the experiment results were undesirable, then the whole experiment has to be repeated again [5].

The discovery and development of a new drug are complex, and the prediction of pharmacokinetics and drug targeting has been a challenge for scientists. It is important to know the biopharmaceutical profile in the discovery and development stages, especially in the early ones. If they know the pharmaceutical profile of the drug, it may be helpful to facilitate the preclinical and clinical development processes [6].

Introducing a new drug to market is a complicated process that costs a lot of money, time, and energy. It has been stated that drug discovery and development take about 10−14 years and cost more than one billion dollars. So, to save money and time, computational approaches have been implemented in the processes of drug design, discovery, and development. The computer-aided drug design (CADD) method (Table 18.1) is mostly used for new drug design approaches. "By using CADD, they can reduce the cost of drug discovery and development by up to 50%." Also, the CADD method increases the efficiency of drug discovery and development. CADD employs the usage of programs to find a standard to relate activity to structure; mainly, there are two types of approaches: structure-based drug design (direct) and ligand-based drug design (indirect), which are powerful and efficient techniques [7].

Physico-Chemical Aspects of Dosage Forms and Biopharmaceutics. DOI: https://doi.org/10.1016/B978-0-323-91818-3.00017-7

TABLE 18.1 Computer-aided drug design implications in newly discovered drugs during past two decades.

Generic name of drugs	Year of approval	Discovery assisted by	Pharmacological activity
Lopinavir	2000	SBDD	Antiviral
Imatinib	2001	SBDD	Antineoplastic
Erlotinib	2004	SBDD	Antineoplastic
Sunitinib	2006	SAR and homology modeling	Anticancer
Aliskiren	2007	SBDD and docking	Antihypertensive
Nilotinib	2007	SBDD	Anticancer
Rivaroxaban	2011	HTS, SBDD and Virtual SAR	Anticoagulant
Dolutegravir	2013	Pharmacophore modeling	Antiviral
Grazoprevir	2016	SBDD and docking	To treat Hepatitis C
Acalabrutinib	2017	SAR, SBDD and docking	Anticancer
Copanlisib	2017	SBDD and LBDD	Anticancer
Vaborbactam	2017	Docking and MD	Antibiotic
Apalutamide	2018	SAR and SBDD	Anticancer
Dacomitinib	2018	Combined FBDD and SBDD	Anticancer
Duvelisib	2018	SBDD and LBDD	Anticancer
Lorlatinib	2018	SBDD	Anticancer
Darolutamide	2019	Docking and MD	Antiandrogenic
Erdafitinib	2019	Combined FBDD and SBDD	Anticancer

In this chapter, we are giving an overview of the history and developments of computer-aided biopharmaceuticals.

Simulation tools were first employed in the petrochemical and chemical industries in the early 1960s. They were mainly used to model continuous processes as well as certain transient behaviors of these processes (e.g., startups, shutdowns, and disruptions). The first tool was called BATCHES, and it was launched in the mid-1980s, by Batch Process Technologies. In the mid-1990s, Aspen Technology (a provider of software and services for process industries in Burlington, Massachusetts, USA) proposed Batch Plus, which was later known as Aspen Batch Process Developer. In the same period, Intelligen Inc. (a provider of process simulation and production scheduling tools located in Scotch Plains, New Jersey, USA) proposed SuperPro Designer, which has been developed to target bioprocessing. As its goal has been reached, the focus has changed to assist in the modeling of fine chemicals, pharmaceuticals, food processing, and other types of batch or semicontinuous processes [8].

18.2 Computational biopharmaceutics

Computational biopharmaceutics, which includes artificial intelligence (AI) and multiscale modeling techniques, provides opportunities to change our current formulation strategies. This type of method was able to reveal physical, chemical, mathematical, and other details based on data that extends to polymorphism, chemical stability, formulation screening, and precision medicine. These computational methods mainly involve quantum mechanics (QM), physiologically based pharmacokinetic modeling, simulation of molecular dynamics, process simulation, mathematical modeling, machine learning algorithms, and artificial intelligence (AI). All these together can help in forecasting a molecule's structure and physico-chemical attributes, simulating the motion of molecules and atoms, characterizing the substances structurally, dynamically, and energetically, and examining the molecular mechanisms of molecular mechanics-based formulations. To construct a quantitative formulation prediction model, machine learning algorithms and artificial intelligence have been improved to be capable of producing predictions based on vast volumes of experimental data. AI systems can also help speed up the preformulation process, improve formulations, reduce running costs, and maintain unique knowledge. All the above-mentioned methodologies have become more widely used in pharmaceutical research

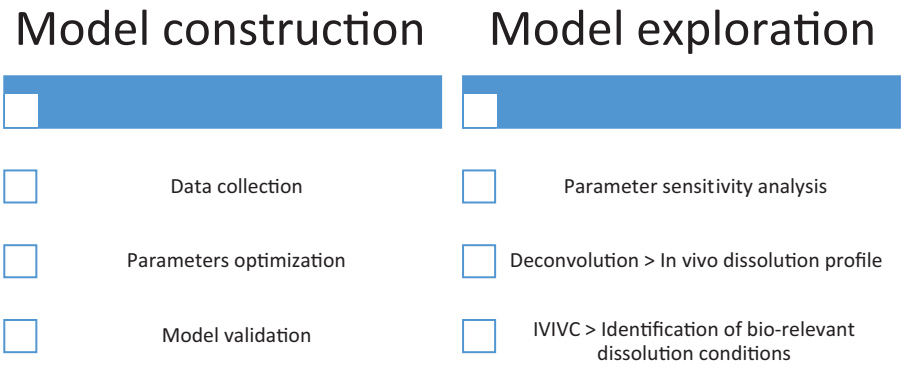

FIGURE 18.1 General modeling and simulation strategy of gastrointestinal (GI) simulation.

in the last few decades. AI is currently being used in a variety of industries, including banking, retail, and medicine. Also, AI has been claimed to be utilized in medication research and development at several stages, including clinical trials, toxicological studies, and the development of active pharmaceutical ingredients [9]. The impact of AI on drug discovery has been illustrated in Fig. 18.1. Many of the world's largest pharmaceutical corporations have at least one AI-based application. This trend has even caught the attention of tech companies like Google and Microsoft. A significant branch of AI, which is machine learning, can match high-dimensional nonlinear correlations to determine the impact of modest input variance on the difference between desired labels. Lately, DeepMind's (AlphaFold2) protein structure prediction tool stunned the world with its experiment accuracy, demonstrating the power of AI paired with biological science and pharmacology [10]. In pharmaceutical research, artificial intelligence is not a new concept. A study performed by Hussain et al. in 1991 [11] used an artificial neural network (ANN) as a powerful pattern recognition classifier that is inspired by the structure and learning capabilities of biological neuron cells. This approach had been developed to identify drug release and dissolution patterns. The accuracy of ANN was shown to be higher than that of classical response surface methods, most likely due to ANN's higher data-fitting capacity. Some benefits that were harvested from AI technologies include reducing formulation duration and guaranteeing that products are of high quality. Unfortunately, there was a prevalent problem when applying machine learning algorithms, which was information insufficiency. This problem was due to the high expense of pharmaceutical tests as well as the length of time required for research and optimization. Because huge pharmaceutical corporations tend to keep their data under lock, current data has become out of reach. Individuals were also looking for a way to understand the operating process underlying machine learning models, rather than the models' strong performance alone, because understanding this process will provide us with more in-depth information in this industry. Computational methods that were engaged in predicting drug solubility profiles, solubilization procedures, and partitioning are applied with traditional molecular simulation techniques. In addition, they allows for a complete understanding of not only solubility but also the various variables and atomic-level interactions that are necessary for the solubilization process. It is a useful technique for evaluating compounds before they are synthesized. Moreover, it should be noted that studying solid properties with simulation models is sometimes difficult, but learning about relative solubility along with calculated solvation free energy makes it easy to calculate absolute solubility in a new solvent [12].

18.3 Computer-aided biopharmaceutical model development

Technologies and computational methods are changing aspects of how pharmaceutical industries will develop in the future. This increases the necessity to update various available in silico tools in the field to find a clue as to where we are and how we go further. In-silico screening models have been widely used in the research and development of biopharmaceuticals, such as gastrointestinal absorption simulation, in silico computational modeling, monoclonal antibodies, predicting the corneal permeability of some medicinal agents, and the identification of potential compounds to treat diseases [13].

18.3.1 Gastrointestinal absorption simulation

In the early stages, biopharmaceutical evaluation of drugs was confined to preclinical and clinical assessment; in later stages, in-silico models were introduced to predict not only drug absorption but also the effect of many factors, such as drug physiochemical properties, on the drug's performance, mainly the pharmacokinetics of orally administered drugs.

This process was not easy at all due to the complexity of drug absorption in the gastrointestinal tract. Many approaches were introduced, at first the pH-partition hypothesis and then the complex Compartmental Absorption and Transit (CAT) model, which represent both steady-state and dynamic models [14]. After that, new dynamic models were instructed to show and present the physiology of the gastrointestinal tract, considering drug dissolution and absorption. These in silico models are the Grass model, Advanced Dissolution, Absorption, Metabolism (ADAM), CAT, Advanced CAT (ACAT), and the GI-Transit-Absorption (GITA) models. These dynamic approaches have been used to predict the drug absorption rate, the fraction of the absorbed dose, and plasma concentration-time profiles. The goal of such models was to enhance the bioavailability of oral drugs using in silico simulation before being introduced to in vivo studies; consequently, both time and cost are reduced using in silico models compared to in vivo studies. In addition, these models can be applied to scout about mechanistic hypotheses, so the effect that the food has on drug absorption will be minimized. Also, when the drug has low solubility and shows nonlinear kinetics and PK analysis is limited, in-silico simulation is a great choice [15]. The general modeling and simulation strategy of GI simulation is represented in Fig. 18.1.

GastroPlus simulation software is a physiologically based pharmacokinetic (PBPK) model that uses the ACAT model to simulate the human absorption of oral drugs and formulations and predict the pharmacokinetics and pharmacodynamics of drugs absorbed through the gastrointestinal compartments [16]. This model is composed of nine compartments that represent different parts of the GI tract, which are the stomach, duodenum, two jejunum compartments, three ileum compartments, cacum, and ascending colon. These compartments are subdivided to include drugs that are undissolved, dissolved, unreleased, and absorbed. Each process is set by a rate constant called the transfer rate constant (Kt), a series of parameters based on different conditions like pH, drug concentration, etc. in that compartment at that moment, as well as the dissolution rate constant (Kd) and absorption rate constant (Ka). When the drug passes through the GI tract, it undergoes changes in the physiological conditions like paracellular and transcellular changes, pH, and surface area; therefore, it will cause changes in the permeability and absorption rate. These changes can be controlled by the Absorption Scale Factor (ASF). The ASF values are estimated on a logD model basis. This model indicates that the permeability decreases when the ionized fraction of the compounds increases. The formulation types used are tablets, suspensions, and capsules. In Gastroplus, the gastric transit time for these formulations differs; for tablets, it's 15 minutes, but for suspensions and capsules, it's 6 minutes. Each version of the software uses a default gastric time and a different type of formulation. GastroPlus simulations were carried out using a 70 kg body weight and no enterohepatic recirculation. In addition to the transport pathways, the ACAT model allows presystemic metabolism. Transcellular transport was only used as there was no available information about paracellular transport in this model, and most of the compounds are highly lipophilic. This commercial software gives an automatic prediction of the fraction of dose absorbed (Fa) in the fasted and fed states [17]. Table 18.2 presents a list of commercial ADMET modeling software.

After the medicinal substance arrives in the liver and undergoes a first-pass effect, where the bile salts interfere with its solubility, it will enter the blood circulation, where the ACAT model can predict liver metabolism, describe the drug distribution and absorption in the tissues, and describes its dissolution kinetics by Noyes-Whitney equation modification

TABLE 18.2 List of available commercial ADMET modeling programs.

Software	Developer	Applications
ADMET Predictor	Simulation Plus, Inc.	ADMET prediction
StarDrop	Optibrium, Ltd	ADMET prediction
ADME Suite	Advanced chemistry development, Inc.	ADMET prediction
Toxsuite	Advanced chemistry development, Inc.	Toxicity prediction
ADMEWORKS Predictor	FujitsuFQS	ADMET prediction
OikProp	Schrodinger, Inc.	ADMET prediction
MetaDrug	GeneGo, Inc.	Metabolism and ADMET Prediction
TOPKAT	Accelrys, Inc.	Toxicity prediction
PASS	Russian Academy of Medical Sciences	Toxicity prediction
METAPC CASETOX	Multicase, Inc	Metabolism and ADMET Prediction

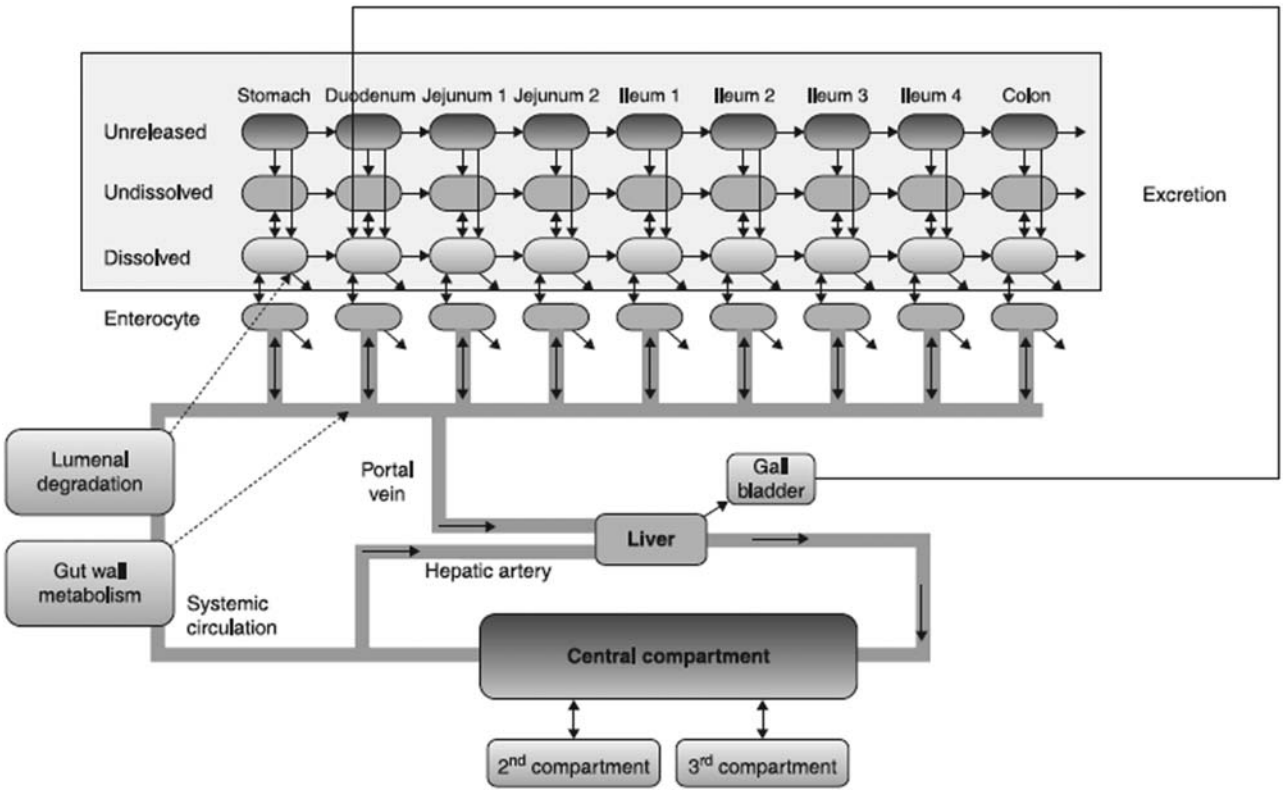

FIGURE 18.2 Advanced compartmental absorption and transit model interpretation of in vivo drug behavior (according to SimulationPlus, Inc. GastroPlus version 8.0 manual).

by Nernst−Brunner. The Gastroplus ACAT model provides a good description, especially for BCS class 1 substances; however, the model must be provided with more data input about permeability and solubility to predict the substances of other BCS classes [18]. Using this model, we can also obtain a clearer mechanistic understanding of the compound's features and human pharmacokinetics (PK) and study the reasons for poor oral bioavailability. The steps of model construction are collecting data, optimizing parameters, and validating the model. These models require a great deal of input data, and comparison studies between different models are still lacking. Fig. 18.2 presents the ACAT model interpretation of in vivo drug behavior as per SimulationPlus, Inc.'s GastroPlus version 8.0 manual.

A project known as OrBiTo uses the PBPK models, Gastroplus, GI-sim and SimCyp softwares. These models use the physiochemical properties of drugs in vitro to predict many pharmacokinetic parameters, such as area under the curve (AUC), maximum plasma concentration (Cmax), and oral absolute bioavailability (F oral) in humans. SimCyp is a software simulator that uses the ADAM model, which considers the gastrointestinal tract as one colon, one stomach, and seven SI compartments. The model shows the effects of dissolution rate and solubility on luminal pH and the concentration of bile salts. The Henderson- Hasselbalch equation is applied to describe the solubility. GI-Sim. In this software, there may be a partitioning process for dissolved, unchanged molecules into colloidal structures. The degree of this process is based on the relationship between the drug solubility in biorelevent dissolution media and that in the buffer. The equation of Henderson−Hasselbalch also describes the pH-dependent solubility [19]. As a conclusion, many studies show that Gastroplus and GI-Sim gave better results than SimCyp in predicting GI absorption of drugs. Fig. 18.2 shows the nine compartments that make up the ACAT model of the human GI tract, each of which represents a distinct section of the GI tract (stomach, duodenum, two jejunum compartments, three ileum compartments, cacum, and ascending colon). The drug that is unreleased, undissolved, dissolved, and absorbed is separated into four more compartments (entered into the enterocytes). Differential equations are used to model the movement of the medication between each subcompartment. In each GI compartment, ten processes collectively determine how quickly the concentration of dissolved drugs changes.

Jones et al. used PBPK absorption modeling across several species to establish a novel method for forecasting human pharmacokinetics in the fasting and fed stages [20]. According to the suggested approach, the absorption models are initially created for the preclinical species of choice (such as mice, rats, dogs, and monkeys) using data collected

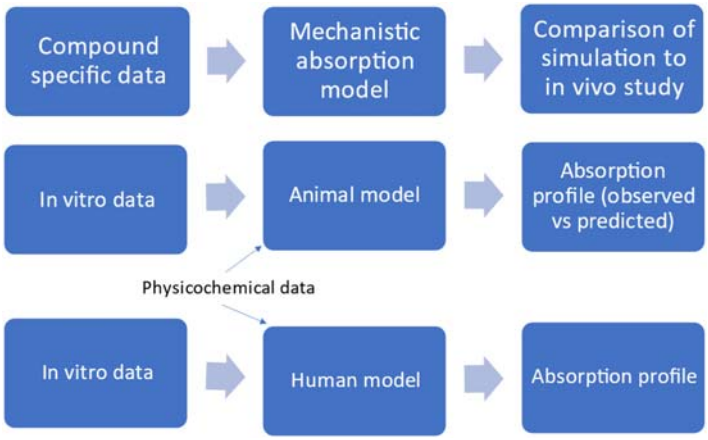

FIGURE 18.3 Physiologically based pharmacokinetic prediction strategy for oral absorption prediction.

during drug research and preclinical development and are then thoroughly verified by comparing the simulation results with those of in vivo animal studies. The PBPK prediction strategy for oral absorption prediction is shown in Fig. 18.3.

For theophylline, a BCS class I substance, the default GastroPlusTM models for both dogs and humans could accurately mimic the dietary effects for both immediate and continuous release formulations [21]. However, many modifications to the standard GastroPlusTM models were necessary for simulations for the BCS II medication aprepitant. In view of the complexity of the described GastroPlus model and the number of data points required for simulation, it is evident that the reliability of the modeling results is dependent on both the model and the selected data set. Therefore, the necessary input data has to be carefully selected and/or experimentally verified. However, with the right selection of input data, a well-validated absorption model, and the correct interpretation of modeling results, GI simulation shows great promise in assessing the biorelevant features of formulated drugs.

18.3.2 In silico computational modeling

In recent years, there has been a noticeable increase in the number of prospective medications that are being synthesized. These medications may not work as well as they should or have poor target binding because of poor absorption, unsuitable distribution, or a quick metabolism. The development of new drugs has emphasized selectivity and efficacy against biological targets. Due to adverse drug pharmacokinetic features such as suboptimal drug absorption, distribution, metabolism, excretion, and toxicity, about 50% of drug candidates in phase II and phase III clinical trials fail (ADMET). Early in the drug discovery process, in vitro examination of ADMET properties has gained popularity as a cost-saving measure. Caco-2 and Madin-Darby Canine Kidney (MDCK) cell monolayers are widely used to simulate membrane permeability and calculate in vivo absorption. Therefore, it is crucial to examine their ADME traits to make sure the medication is efficient and secure. In vitro ADME screening is not cost-effective and cannot keep up with the rising number of new medications. In silico models may now be trained and used to forecast the ADMET properties of medications even before they are ever created as a result of these in vitro studies. There have been tremendous advancements in silico modeling tools, and computational programs that simulate drug ADMET properties are widely available [22].

18.3.2.1 Predicting corneal permeation using the quantitative structure property relationship approach

The topical route is the easiest route for ophthalmic administration, but several factors restrict corneal permeation, such as lacrimation, pH, short contact time, and reflux tearing mechanisms. This explains the importance of developing an ophthalmic-specific drug delivery system to enhance therapeutic efficacy. In drug discovery, there are abundant techniques that utilize in-silico-based methods to accelerate the optimization step. Among these techniques, we have the Quantitative Structure Property Relationship (QSPR) approach [23].

The QSPR approach combines both the biological activity of a molecule and its physico-chemical properties through a diversity of descriptors. This method was used in designing models specified to predict drug permeation through the different barriers, such as the blood, intestine, and central nervous system. Medications, which are designed for ocular delivery, were originally developed from oral or systemic medications. Few drugs have been developed and investigated as ocular-specific delivery systems. Fluoroquinolones are the drug of choice in cases of ophthalmic disorders. Because

of their broad-spectrum activity, bactericidal property, better ocular penetration, and safety profile, their use has escalated in ophthalmology. But unfortunately, existing data lacks important information like understanding their corneal toxicity, corneal permeability, usage frequency, and contact time. Thus, the use of the QSPR methodology to improve the pharmacokinetic profile and therapeutic efficacy is eligible [24]. Former QSPR models that were applied to predict drug corneal permeation have been founded based upon in vitro studies. In 2010, Kidron et al. used the QSPR method based upon in vitro information to construct a new model for corneal permeation. They tested a total of 58 different molecules in the cornea of rabbits' eyes. The study was done with the use of Ringers' buffered solution for 6 hours, the degree of hydration was less than 83%, and they used a mixture of oxygen and carbon dioxide (CO_2) to control the level of pH at a temperature of 34°C−37°C. He concluded that the most critical factors for permeation were logD at physiological pH and the maximum number of hydrogen bonds that can be created [25]. It is assumed that there is poor engagement between the in vitro and in vivo studies, which limits the applicability of these models to predict corneal drug permeation. This necessitated the development of novel QSPR models capable of predicting corneal drug permeability. Sharma et al. reported the development of a novel QSPR model to predict the corneal drug penetration of fluoroquinolones. According to the literature, there are two models used to correlate the corneal permeation of medicinal agents with their physiochemical properties; the first one was developed by Yoshida and Topliss [26], and it is based on two molecular descriptors, Δlog P and log D, to predict the corneal permeability. The second model was developed by Fu and Liang, and it is based on charge and molecular volume as molecular descriptors. The applicability of these two models to predict fluoroquinolone corneal permeation was estimated and found to be unsuitable since these predictive approaches have been derived based on various in vitro studies [27]. The Cassette dosing model has been employed to determine the in vivo corneal permeability in test animals. This approach, also known as "cocktail or N-in-one dosing," is described as a process that uses high-throughput screening (HTS) in the discovery of drugs to speedily recognize potentially useful compounds and abolish those with bad pharmacokinetic properties. A single animal is given a combination of compounds of the same structural species at very low doses [28]. For this study, nine types of fluoroquinolones were casually sectioned into two sets; each one was dissolved at a concentration of 0.1%, and the aqueous medium was boric acid mixed with water. All the experiments were done according to the Association for Research in Vision and Ophthalmology (ARVO), as they approved the use of animals in ophthalmic studies. A sterile mixture of both groups was administered to rabbit eyes; after that, topical anesthesia was carried out using an anterior chamber paracentesis. At specified time points, humor samples were collected from the surface of the cornea and stored at −80°C. Researchers used a chromatographic technique called high-performance liquid chromatography (HPLC) to quantify the fluoroquinolones present in the samples. The standard accuracy variables for this experiment were found to be in the allowed range as stated by the ICH regulations for HPLC used in biosynthesis. A new QSPR model that consisted of four new algorithms was derived using the difference in energy between E_HUMO (electron donating)−E_LUMO (electron accepting) (GAP), partition coefficient (logP), topological polar surface area (TPSA), and dissociation constant (pKa) as molecular descriptors. These factors are known to influence permeation through the cornea. In this approach, the trans-corneal penetration was based on in vivo permeation parameters, thus showing a high degree of applicability and acceptability compared to the earlier models. Furthermore, this approach showed the capability to predict the corneal permeation of congeneric β-blockers, as it has been reported in the literature, and further studies were performed to evaluate it with other medicinal agents [29].

18.3.2.2 Structural prediction of ligand-binding site for monoclonal antibodies

Immunoglobulins are proteins composed of two polypeptide chains: a light chain and a heavy chain; both of them contain two and four domains, respectively, held together by a disulfide link and nonbounded hydrophobic contact [30]. All immunoglobulins in the body have an antigen-binding site; this binding site contains "hypervariable residue," which is termed the complementary determining regions (CDR). This region gives antigen specificity for a given antibody. By computer-aided molecular modeling (CAMM), we can determine the amino acid sequence of the antibody structure. The prediction of an antibody fragment's structure will help to demonstrate the unique structure of immunoglobulin and the specificity of antigen recognition. CAMM has been used to predict the ligand-binding site of the monoclonal antibody NC6.8, which has high affinity and can bind to the superpotent sweetener ligand N-(*p*-cyanophenyl)-N′-(diphenyl methyl) guanidine acetic acid. The principle of these methods has been the comparison of antibodies that are desired to be modeled with a known sequence of a 3D structure in the database; the antibody with the most similar arrangement is selected as a platform for homology design. One major problem in CAMM is the large diversity in size and structure of CDR loops with distinct antibodies. Results from other resources that were obtained to confirm the CAMM project, such as pH titrations of radio-ligand linkage, spectroscopy, and competitive analog radio-immunoassays [31].

Different programs in computer-aided design were used to model and determine the FV (variable domain fragment), ABalign, and ABbuild of the ABGEN algorithm and have been used to produce the first order Fv model. The H- and L-chain sequences of the variable domain fragment in the monoclonal antibody NC6.8 are separated into four Framework Regions (FR) and three Complementary Determining Regions (CDR). The FR contain the most conserved part; these regions occur precisely at the same positions in all immunoglobulin sequences. In order to encompass the increasing numbers of antibodies, the need for a database that presents antibodies aligned in sequences is necessary. KABAT et al. introduced the KABAT database, which contains a numbering scheme and is not just a sequence library but can also integrate essential parts of our immune system. The KABAT database is available on the Internet using the formula File Transfer Protocol (FTP) [32].

18.3.2.3 Optimization of a highly viscous antibody by computer-aided design

Increased attention has been focused recently on treatment using antibodies, and this can be observed with the increased number of approved antibody medications in the United States and Europe. Therapeutic antibodies are proteins that are administered subcutaneously, as they cannot be given orally due to their large size and biophysical properties, to elicit an effective therapeutic effect. Some factors must be considered during the development of these medications, such as solubility and viscosity. The viscosity is usually preferred to be less than 20 centipoises (cP) for minimal pain and optimal syringeability [33]. It has been noticed that a reduction in the viscosity of antibodies can be achieved by charge-change mutations. Three computationally aided models have been used to predict the antibody's viscosity based on its structural information. Sharma et al. [34] examined the relationship between the antibody's viscosity and FV (variable domain fragment) charge, asymmetry charge, and hydrophobic properties. They stated that an increase in hydrophobicity and the net negative charge would increase the viscosity. This protocol has been explored into an equation described by the Sharma method to predict the antibody's viscosity (Eq. 18.1), where η represents the viscosity and is related to the hydrophobic index (HI), the net charge of the Fv (q), and the charge asymmetry (qsym).

$$\eta = 10^{0.15+1.26\times HI-0.043\times q-0.02\times qsym} \tag{18.1}$$

Firstly, the net charge of the variable loops of the antibody VH and VL sequences is calculated by summing of Asp, Glu, His, Lys, and Arg charges. The charge asymmetry is calculated by the VL and VH summation products. Finally, the hydrophobic index (HI) is calculated by the ratio of the hydrophobicity of hydrophobic parts to the hydrophobicity of hydrophilic parts. Tomar et al. [35] employed the support vector machine (SVM) model in predicting the viscosity of different antibodies. In this model, it has been observed that the FV (variable domain fragment) charge has an important effect on hydrophobicity, considering a change in viscosity. To apply this protocol, they generate the IgG homology model using the protein modeler tool in the molecular modeling software package MOE with FV templates, thus facilitating the determination of the variable loops of antibody and hydrophobic solvent surface area. Then use these values in Eq. 18.1 to predict the viscosity. Agrawal et al. [36] developed a spatial charge map (SCM) tool to examine the relationship between the viscosity of antibodies and the extent and magnitude of a negative charge in FV. In the SCM protocol, a homology model of the FV domains of the charged antibodies has been used to predict their viscosity. They applied these principles to optimize a highly viscous antiPDGF-BB (platelet-derived growth factor B homodimer) antibody while maintaining its binding affinity and effectiveness. The viscosity was found to be 40 cP at 98.8 g/L, while the extrapolated value is 250−300 cP at 150 g/L. The main aim of this study was to decrease the viscosity to less than 20 cP at high concentrations (>150 g/L).

18.3.2.4 In-silico model for pulmonary sensitization

The Cosmetics Directive in the European Union (EU) has prohibited testing new cosmetic ingredients on animals. Given the widespread usage of low-molecular-weight (LMW) compounds (known as any matter that possesses a molecular mass of less than 1000 g/mol) in the cosmetics sector and the hardship of animal testing, such legislation is critical. It is equally critical that this policy does not come at an excessively large financial cost; therefore, the adverse outcome pathway (AOP) concept arose from the necessity to establish alternative, nonanimal test techniques for chemical safety evaluation [37]. The focus of AOP is to explain the main processes that may be tested utilizing in-silico, in-chemico, or in-vitro methodologies rather than to outline every minute detail of the biological pathway that is disrupted, leading to toxicity. In-silico techniques have concentrated on characterizing the chemistry related to the early interaction between a chemical and a biological system within the AOP model, and it was named "Molecular Initiating Event" (MIE). The chemistry coupled with MIEs can be gathered into 'in-silico profilers,' which allow chemicals to be categorized into groups based upon their mechanisms, allowing for toxicity predictions. Furthermore, rather than testing every molecule,

such profilers allow chemical inventories to be highlighted for future in-vitro or in-chemico investigations. Scientists working on novel cosmetic items are particularly interested in a chemical's capacity to create skin or respiratory sensitization. A person can react to an LMW substance firstly through skin or inhalation (the induction phase); with the second exposure (the elicitation phase), toxicity is observed, so it is crucial to be able to estimate the possibility of cutaneous and respiratory sensitization, knowing that once a person's immune system has become sensitized to a toxin, they may remain so for the rest of their existence. Existed data from some experiments gave the researchers a major mechanistic conclusion about skin sensitization; these data were presented as an AOP. The AOP lays out the proof that the molecular initiating event (MIE) for skin sensitization is the establishment of a covalent connection between an LMW substance and a protein. The development of various in-silico profilers has been enabled by mechanistic data along with the existence of toxicological information; on the other hand, information about respiratory sensitization is not clarified due to a lack of reliable animal testing [38]. This kind of data is desired to create an accurate in silico analyzer for pulmonary sensitization. The analyzer for pulmonary sensitization was joined together with the new edition of the OECD QSAR, and it was created using information about a group of LMW compounds along with their mechanistic chemical study. The main concern in the present experiment was to emphasize the MIE of pulmonary sensitizers, which was implicated in binding covalently in the lungs. At last, the study then gathered two important elements for MIE in the process of pulmonary sensitization, which are electrophilicity and the capability to bind proteins. Furthermore, researchers proposed that when the substance is sufficiently electrophilic (such as cyanoacrylates), it can cause sensitivity without even binding to proteins. On the other hand, when a molecule is not as electrophilic (such as di-isocyanates), it requires several reactive sites leading to protein binding. Previous data claimed that every molecule that causes pulmonary sensitivity should have various reactive sites. Accessibility of information related to pulmonary sensitivity allowed the researchers to expand their investigation, which permitted them to summarize the mechanistic chemistry of LMW compounds in details. This kind of data also gave them the opportunity to examine areas in chemical fields that were unknown [39].

18.3.2.5 The use of computer-aided designing in the creation of oncolytic virus and for overcoming challenges of cancer immunotherapy

Cancer is a disease in which cells grow abnormally and may spread to other parts of the body. A tumor inside the body is surrounded by an ecosystem called the tumor microenvironment (TME). The TME decreases antitumor immunity. According to clinical research, antitumor immunity is an immune response that leads to tumor control, so the control of the tumor microenvironment (TME) is critical for cancer treatment. As a result, they comprehend that immunotherapy is a significant cancer-fighting medicinal technique. T-VEC is the first genetically modified virus that has been approved as an oncolytic virus by the US Food and Drug Administration (FDA). The use of oncolytic viruses as a novel class of cancer immunotherapeutic medicine is gaining traction; this technique is superior to other methods because of its high selectivity for tumor cells and its ability to overcome transcriptional and mutational resistance. By increasing the expression of cytokines and chemokines, the oncolytic viruses destabilize the immunologically repressed TME and attract the innate and adaptive immune cells to the TME both locally and systemically, resulting in immunogenic cell death (ICD). So, they demonstrate novel computational methodologies for improving the oncolytic capability of viruses in cancer treatment. Oncolysis occurs when ocolytic viruses selectively replicate in tumor cells, releasing cell debris and tumor antigens into the tumor microenvironment (TME). Immune cells, such as dendritic cells, are attracted to the released debris and tumor microenvironment (TME), and the released antigens will stimulate the anticancer T and B cell responses [40]. For the effective implementation of oncolytic virotherapy, it necessitates the management of a number of critical challenges, including physical barriers to the immune reaction, safety, replication, and delivery. The route of oncolytic virotherapy into the tumor mass has a significant impact on its efficacy. According to research and clinical studies, they found that direct injection or intratumorally for solid malignancies and intravenous injections for other types of cancer are the preferred ways of oncolytic viruses' delivery. Systemic intravenous injections permit oncolytic viruses to reach metastatic locations via the blood stream and enhance the specific targeting of oncolytic viruses. Another challenge that must be managed is physical barriers, which include tissue-resident macrophages. These macrophages play a homeostatic function, which is the scavenging of macromolecules, debris, and invading pathogens, and they have a rapid response to external stimuli that can be an effective target for cancer therapy. The extracellular matrix proteins in tumor cells limit the intratumoral spread of oncolytic viruses, and to overcome this problem, they use enzymes that degrade the matrix, like proteases, which enable anticancer agents to enter cancer cells safely. Clinical and preclinical studies identify possible questions regarding the safety of oncolytic viruses. Genetic modification is being used to adjust the genome sequences of oncolytic viruses, resulting in significant increase in safety and

effectiveness. Host defense against delivered oncolytic viruses is also a major factor that influences their clinical use. For example, antibodies neutralize the oncolytic viruses. To overcome these antibodies, the use of polymer-coated viruses or the combination of oncolytic viruses with drugs that decreases the immune response are effective. The major impediment to oncolytic viruses that prevents them from reaching their target is the tumor microenvironment, which releases cytokines, chemokines, soluble factors, and various matrix enzymes that promote tumor growth. There are new methods that rely on recombinant oncolytic viruses to overcome the impediment of the tumor microenvironment. To make oncolytic viruses' species more effective for cancer immunotherapy [41], they needed to be modified. First of all, they needed to enhance the delivery of oncolytic viruses to the tumor to increase their efficiency, improve oncolysis, overcome physical barriers, evade the antiviral immune response, and modify the tumor microenvironment. Lately, computation-aided design (CAD) has played a major role in the drug development process, so by using computation-aided design (CAD), they can construct and design new oncolytic viruses. In this paper, we propose different computational methods for modifying oncolytic viruses in order to make them safer, more effective, and have a wide therapeutic index. They use computational methods like ACpred-FL, ACpp, AntiCP, MLACP, Tumor HPD, and ACpred to design anticancer and tumor homing peptides. These peptides have enormous therapeutic effects due to their cell permeation, affinity, high specificity, and minimal drug interaction. Anticancer peptides bind to the tumor cell membrane and can cause necrosis, apoptosis, and pyroptosis, so inserting tumor penetrating peptides into oncolytic viruses has several advantages, as a result they suggest creating an arbitrary peptides display library by predicting tumor penetrating peptides sequences within the viral capsid by various computational tools include; (CellPPb, SkipCPP-Pred, CppPred, KELM-CppPred, and Cppred-RF), if these peptides are more hydrophilic their bioavailability increases, the optimization of their hydrophilicity is primarily experimental and time-consuming, but many computational tools have been developed to help speed up the process, (PROS ll and CcSOL) are the tools for predicting protein solubility. Tumor-associated antigens (neoantigens) are released during oncolysis; these therapeutic components are excellent for cancer immunotherapy. Preclinical studies using neoantigen-based vaccination method show promise in cancer management. Epidisco, Vaxrank, ProTECT, and Pvac are examples of open software for computing neoantigens. Advanced tumors are prone to acquire mutations and develop resistance; tumor cells are less resistant toward oncolytic virotherapy, and because of this feature, they are the perfect carriers for creating multifunctional drugs for cancer immunotherapy. For the prediction of cytokine peptide-based immunomodulators, they use computational approaches (IL17 escan and IL-4 Pred), whereas CDRUG and CancerIN are used to discover immunosuppressive anticancer effects of drugs. There are other computational approaches that can be used to identify the toxicity and allergies caused by oncolytic viruses, and these approaches include ToxinPred, AlgPred, Hemopl, and AllerTop. To summarize, oncolytic viruses have enormous potential in the therapy of cancer, and computer-aided viral therapy plays a crucial role in oncolytic virotherapy. Also the combination of computational approaches and genetic engineering could enhance the effect of oncolytic virotherapy [42].

18.3.2.6 Discrete event simulation tools

The discrete event simulator (DES) is a useful simulation tool used to plan a whole process and assist in decision-making in many sectors. It shapes the entire process as a distinct series of events over time. Each step takes place at a specified second in time and identifies the condition of the process. Decision-making in the biopharmaceutical industry is a crucial step and depends mainly on equipment that can give an idea about the process behavior and aid in representing different sides of drug manufacturing. These simulation tools are utilized in the manufacturing of biopharmaceuticals, particularly in gene therapy (GT). Gene therapy is a novel division in this industry that is used to target specific genetic diseases, such as cancer [43]. According to the FDA, it is defined as a method of treatment that can modulate humans' genes to replace malfunctioning or missing genes. Production processes for genes are complex, costly, and can fail in clinical trials; therefore, most products have not succeeded in entering the market. In spite of the problems and novelty, many scientists have started to employ computational power in designing, simulating, and as a scheduling tool to optimize their knowledge of biotechnology. The computer tools utilized are divided into four groups, which are: mathematical programming, stochastic modeling, optimization, and discrete event simulation. In reality, all of the promoted tools that are used in biopharmaceuticals are a fusion of these categories. The most conventional approach is mathematical coding, which involves creating numerical correlations with variables to express unit operation technically. Equations innovated by simulation tools like "SPEEDUP" by Aspen Tech. are utilized for modeling unit operations in the manufacturing of biopharmaceuticals. A disadvantage to this method is the inability to give an image of these units instantaneously. In order to overcome this problem, they started to involve graphics with it. The use of discrete event simulation (DES) permits undirected and advanced imitation of the whole biopharmaceutical procedure that

is targeted for planning and increasing production capacity, scheduling, and reducing water. Also, it has been shown that DES modeling can help in the maintenance stage and provides flexibility in capturing the dynamics and randomness of GT production processes. Biopharmaceutical mass production has a lot of challenges and problems, so to overcome this complexity, it requires a specified method for the discrete event simulator expansion. Model creation begins with a process map and an awareness of the project's scope. A present model can demonstrate a single manufacturing procedure within a complete framework or contain a variety of activities within one system. Thus, it is considered critical to set the models' borders before starting. It should be noted that simulation software does not guarantee an exact replica of the actual process. A critical step before executing the simulation scenarios is to standardize each one of the models to ensure they provide results that are close to reality [44]. The next phase in model building is to define the constituents in our simulation operator, which illustrates the production line being investigated. These constituents are variables, entities, resources, and attributes, and they are required for simulators' algorithms. The reliability of the simulation results is determined by the data used in model creation. As a result, the model is divided into many modules that represent distinct unit processes to make data gathering, organizing, and evaluation easier. Inside this simulation software, input values are divided into three categories: data about product flow, data about systems' capacity, and data about processes' schedule. The simulation data is then collected, and critical performance metrics are defined [45].

18.4 Concluding remarks

Computational modeling has evolved into a crucial tool that speeds up the formulation development process by providing an effective and affordable technique to evaluate medication bioperformance in a short amount of time. There are still certain limitations, most notably the absence of pertinent data on drug and dosage form parameters needed for precise pharmacokinetic profile prediction. Additionally, one of the reasons why the industry has not yet fully utilized these technologies is because there is a lack of confidence in in silico predictions. It is anticipated that formulation scientists will employ GI modeling more frequently when new data on medication biological characteristics is gathered. In this respect, it should be emphasized that pharmaceutical companies and regulatory organizations still have huge amounts of important data on drug biologic properties, and even limited access to these data would be beneficial to create and/or validate in silico absorption models. Computational absorption modeling is an essential technique that speeds up the formulation development process since it provides a quick and affordable way to evaluate drug bioperformance. There are still several gaps, most notably the absence of pertinent data on drug and dosage form parameters needed for precise drug PK profile prediction. Additionally, one of the reasons why the industry has not yet fully embraced these methodologies is the lack of confidence in in silico predictions. It would also help to promote in silico techniques' wider acceptability if published cases of their successful use.

Acknowledgments

Authors are grateful to the Philadelphia University, Jordan for the generous research funding (project number 511/34/100 PU) and support to author M.F.B.

Consent for publication

Not applicable.

Conflict of interest

The author declares no conflict of interest, financial, or otherwise.

References

[1] Ilango KB, Gowthaman S, Seramaan KI, Chidambaram K, Bayan MF, Rahamathulla M, et al. Mucilage of *Coccinia grandis* as an efficient natural polymer-based pharmaceutical excipient. Polymers (Basel) 2022;14. Available from: https://doi.org/10.3390/polym14010215.

[2] Walsh G. Biopharmaceutical benchmarks 2018. Nat Biotechnol 2018;36:1136–45. Available from: https://doi.org/10.1038/nbt.4305.

[3] Buyel JF, Woo JA, Cramer SM, Fischer R. The use of quantitative structure-activity relationship models to develop optimized processes for the removal of tobacco host cell proteins during biopharmaceutical production. J Chromatogr A 2013;1322:18–28. Available from: https://doi.org/10.1016/j.chroma.2013.10.076.

[4] ter Horst JP, Turimella SL, Metsers F, Zwiers A. Implementation of quality by design (QbD) principles in regulatory dossiers of medicinal products in the European Union (EU) between 2014 and 2019. Ther Innov Regul Sci 2021;55:583–90. Available from: https://doi.org/10.1007/s43441-020-00254-9.
[5] Yu LX, Amidon G, Khan MA, Hoag SW, Polli J, Raju GK, et al. Understanding pharmaceutical quality by design. AAPS J 2014;16:771–83. Available from: https://doi.org/10.1208/s12248-014-9598-3.
[6] Mohs RC, Greig NH. Drug discovery and development: Role of basic biological research, Alzheimer's Dement. Transl Res Clin Interv 2017;3:651–7. Available from: https://doi.org/10.1016/j.trci.2017.10.005.
[7] Medina-Franco JL. Grand challenges of computer-aided drug design: the road ahead. Front Drug Discov 2021;1. Available from: https://www.frontiersin.org/articles/10.3389/fddsv.2021.728551.
[8] Petrides D, Carmichael D, Siletti C, Koulouris A. Biopharmaceutical process optimization with simulation and scheduling tools. Bioengineering 2014;1:154–87. Available from: https://doi.org/10.3390/bioengineering1040154.
[9] Paul D, Sanap G, Shenoy S, Kalyane D, Kalia K, Tekade RK. Artificial intelligence in drug discovery and development. Drug Discov Today 2021;26:80–93. Available from: https://doi.org/10.1016/j.drudis.2020.10.010.
[10] McCoubrey LE, Thomaidou S, Elbadawi M, Gaisford S, Basit AW, Orlu M. Machine learning predicts drug metabolism and bioaccumulation by intestinal microbiota. Pharmaceutics 2021;13. Available from: https://doi.org/10.3390/pharmaceutics13122001.
[11] Hossain S, Kabedev A, Parrow A, Bergström CAS, Larsson P. Molecular simulation as a computational pharmaceutics tool to predict drug solubility, solubilization processes and partitioning. Eur J Pharm Biopharm 2019;137:46–55. Available from: https://doi.org/10.1016/j.ejpb.2019.02.007.
[12] Wu F, Zhou Y, Li L, Shen X, Chen G, Wang X, et al. Computational approaches in preclinical studies on drug discovery and development. Front Chem 2020;8. Available from: https://doi.org/10.3389/fchem.2020.00726.
[13] Sankar M, Ramachandran B, Pandi B, Mutharasappan N, Ramasamy V, Prabu PG, et al. In silico screening of natural phytocompounds towards identification of potential lead compounds to treat COVID-19. Front Mol Biosci 2021;8. Available from: https://doi.org/10.3389/fmolb.2021.637122.
[14] Yu LX, Amidon GL. A compartmental absorption and transit model for estimating oral drug absorption. Int J Pharm 1999;186:119–25. Available from: https://doi.org/10.1016/S0378-5173(99)00147-7.
[15] Balakumar C, Ramesh M, Tham CL, Khathi SP, Kozielski F, Srinivasulu C, et al. Ligand- and structure-based in silico studies to identify kinesin spindle protein (KSP) inhibitors as potential anticancer agents. J Biomol Struct Dyn 2018;36:3687–704. Available from: https://doi.org/10.1080/07391102.2017.1396255.
[16] Zhuang X, Lu C. PBPK modeling and simulation in drug research and development. Acta Pharm Sin B 2016;6:430–40. Available from: https://doi.org/10.1016/j.apsb.2016.04.004.
[17] Daga PR, Bolger MB, Haworth IS, Clark RD, Martin EJ. Physiologically based pharmacokinetic modeling in lead optimization. 1. Evaluation and adaptation of GastroPlus to predict bioavailability of medchem series. Mol Pharm 2018;15:821–30. Available from: https://doi.org/10.1021/acs.molpharmaceut.7b00972.
[18] Gobeau N, Stringer R, De Buck S, Tuntland T, Faller B. Evaluation of the GastroPlusTM advanced compartmental and transit (ACAT) model in early discovery. Pharm Res 2016;33:2126–39. Available from: https://doi.org/10.1007/s11095-016-1951-z.
[19] Bayan MF, Marji SM, Salem MS, Begum MY, Chidambaram K, Chandrasekaran B. Development of polymeric-based formulation as potential smart colonic drug delivery system. Polymers (Basel) 2022;14. Available from: https://doi.org/10.3390/polym14173697.
[20] Jones HM, Rowland-Yeo K. Basic concepts in physiologically based pharmacokinetic modeling in drug discovery and development. CPT Pharmacomet Syst Pharmacol 2013;2:e63. Available from: https://doi.org/10.1038/psp.2013.41.
[21] Arafat M, Sarfraz M, Aburuz S. Development and in vitro evaluation of controlled release viagra® containing poloxamer-188 using gastroplusTM pbpk modeling software for in vivo predictions and pharmacokinetic assessments. Pharmaceuticals 2021;14. Available from: https://doi.org/10.3390/ph14050479.
[22] Lombardo F, Desai PV, Arimoto R, Desino KE, Fischer H, Keefer CE, et al. In silico absorption, distribution, metabolism, excretion, and pharmacokinetics (ADME-PK): utility and best practices. An industry perspective from the international consortium for innovation through quality in pharmaceutical development. J Med Chem 2017;60:9097–113. Available from: https://doi.org/10.1021/acs.jmedchem.7b00487.
[23] Wadhwa P, Mittal A. Quantitative structure-property relationship (QSPR) modeling applications in formulation development. In: Saharan VA, editor. Computer aided pharmaceutics and drug delivery. Singapore, Singapore: Springer Nature; 2022. p. 543–60. Available from: https://doi.org/10.1007/978-981-16-5180-9_17.
[24] Buglak AA, Charisiadis A, Sheehan A, Kingsbury CJ, Senge MO, Filatov MA. Quantitative structure-property relationship modelling for the prediction of singlet oxygen generation by heavy-atom-free BODIPY photosensitizers**. Chem-A Eur J 2021;27:9934–47. Available from: https://doi.org/10.1002/chem.202100922.
[25] Kidron H, Vellonen KS, Del Amo EM, Tissari A, Urtti A. Prediction of the corneal permeability of drug-like compounds. Pharm Res 2010;27:1398–407. Available from: https://doi.org/10.1007/s11095-010-0132-8.
[26] Yoshida F, Topliss JG. QSAR model for drug human oral bioavailability. J Med Chem 2000;43:2575–85. Available from: https://doi.org/10.1021/jm0000564.
[27] Velpandian T, Sharma C, Biswas NR, Nayak N, Vajpayee RB, Ghose S. Development of novel in silico model to predict corneal permeability for congeneric drugs: a QSPR approach. J Biomed Biotechnol 2011;2011:483869. Available from: https://doi.org/10.1155/2011/483869.
[28] Hughes JP, Rees SS, Kalindjian SB, Philpott KL. Principles of early drug discovery. Br J Pharmacol 2011;162:1239–49. Available from: https://doi.org/10.1111/j.1476-5381.2010.01127.x.

[29] Ghemtio L, Xhaard H, Urtti A, Kidron H. Predictive modeling of ocular pharmacokinetics and adverse effects. Curr Pharm Des 2016;22:6928–34. Available from: https://doi.org/10.2174/1381612822666160923120244.

[30] Saadh MJ, Sa'Adeh IJ, Dababneh MF, Almaaytah AM, Bayan MF. Production, immunogenicity, stability, and safety of a vaccine against *Clostridium perfringens* beta toxins. Vet World 2020;13:1517–23. Available from: https://doi.org/10.14202/vetworld.2020.1517-1523.

[31] Chai S, Song Z, Zhou T, Zhang L, Qi Z. Computer-aided molecular design of solvents for chemical separation processes. Curr Opin Chem Eng 2022;35:100732. Available from: https://doi.org/10.1016/j.coche.2021.100732.

[32] Johnson G, Te Wu T. Kabat database and its applications: 30 years after the first variability plot. Nucleic Acids Res 2000;28:214–18. Available from: https://doi.org/10.1093/nar/28.1.214.

[33] Apgar JR, Tam ASP, Sorm R, Moesta S, King AC, Yang H, et al. Modeling and mitigation of high-concentration antibody viscosity through structure-based computer-aided protein design. PLoS One 2020;15:e0232713. Available from: https://doi.org/10.1371/journal.pone.0232713.

[34] Sharma VK, Patapoff TW, Kabakoff B, Pai S, Hilario E, Zhang B, et al. In silico selection of therapeutic antibodies for development: viscosity, clearance, and chemical stability. Proc Natl Acad Sci USA 2014;111:18601–6. Available from: https://doi.org/10.1073/pnas.1421779112.

[35] Tomar D, Agarwal S. Twin support vector machine: A review from 2007 to 2014. Egypt Inform J 2015;16:55–69. Available from: https://doi.org/10.1016/j.eij.2014.12.003.

[36] Agrawal NJ, Helk B, Kumar S, Mody N, Sathish HA, Samra HS, et al. Computational tool for the early screening of monoclonal antibodies for their viscosities. mAbs 2016;8:43–8. Available from: https://doi.org/10.1080/19420862.2015.1099773.

[37] Golden E, Maertens M, Hartung T, Maertens A. Mapping chemical respiratory sensitization: how useful are our current computational tools? Chem Res Toxicol 2021;34:473–82. Available from: https://doi.org/10.1021/acs.chemrestox.0c00320.

[38] Dakkah AN, Bataineh Y, Jaidi BAA, Bayan MF, Nimer NA. Nanomedicines in tuberculosis: diagnosis, therapy and nanodrug delivery. In: Krishnan A, Chuturgoon A, editors. Engineering materials. Cham: Springer International Publishing; 2020. p. 357–404. Available from: https://doi.org/10.1007/978-3-030-36260-7_13.

[39] Enoch SJ, Roberts DW, Madden JC, Cronin MTD. Development of an in silico profiler for respiratory sensitisation. ATLA Altern Lab Anim 2014;42:367–75. Available from: https://doi.org/10.1177/026119291404200606.

[40] Lathwal A, Kumar R, Raghava GPS. Computer-aided designing of oncolytic viruses for overcoming translational challenges of cancer immunotherapy. Drug Discov Today 2020;25:1198–205. Available from: https://doi.org/10.1016/j.drudis.2020.04.008.

[41] Chandrasekaran B, Saravanan M. Editorial: pharmacological and biochemical perspectives of kinase inhibitors in cancer and COVID-19 therapeutics, volume I. Front Pharmacol 2022;13:916324. Available from: https://doi.org/10.3389/fphar.2022.916324.

[42] Cui W, Aouidate A, Wang S, Yu Q, Li Y, Yuan S. Discovering anti-cancer drugs via computational methods. Front Pharmacol 2020;11. Available from: https://doi.org/10.3389/fphar.2020.00733.

[43] Sachidananda M, Erkoyuncu J, Steenstra D, Michalska S. Discrete event simulation modelling for dynamic decision making in biopharmaceutical manufacturing. Procedia CIRP 2016;49:39–44. Available from: https://doi.org/10.1016/j.procir.2015.07.026.

[44] Forbus JJ, Berleant D. Discrete-event simulation in healthcare settings: a review. Modelling 2022;3:417–33. Available from: https://doi.org/10.3390/modelling3040027.

[45] Yauger SJ, Konopasky A, Battista A. Reliability in healthcare simulation setting: a definitional review. Cureus 2020;12:e8111. Available from: https://doi.org/10.7759/cureus.8111.