CHAPTER

Computational pharmaceutics

14

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14.1 Introduction

The science of pharmaceutics is concerned with converting a novel molecular entity (NME) into a drug in the appropriate dosage form for usage by patients [1]. The traditional method of research involves preformulation, formulation, and in vivo investigation based on trial-and-error experiments. This method is time-consuming, expensive, and less effective [2]. Wang et al. (2021) found that it takes approximately 15 years and up to 2558 million dollars to introduce a single NME to the market [2]. Computational pharmaceutics, which applies computers to pharmaceutical medication delivery and modeling (computer simulation), has emerged. This new discipline is less time- and money-consuming than the traditional approach [1]. The computer simulation can model difficult systems which may cost a lot of money and may be complex by providing multiscale lenses to the pharmaceutical scientists, showing all the chemical, physical, and mathematical information that provides the details of chemical stability, formulation, polymorphism, and the precise medicine [2].

Artificial intelligence (AI), molecular dynamics (MD), which is a simulation used to calculate the motion of atoms or molecules, and physiologically based pharmacokinetics modeling (PBPK), which is a mathematical modeling of absorption, distribution, metabolism, and excretion, all depend on computational pharmaceutics. Quantum mechanics (QM) is a theory that describes the physical properties of nature at atomic and subatomic scale particles by the Schrodinger equation.

By using computational methods, we speed up the development, save time and money, and modify the formula to get the optimal drug with good solubility, absorption, stability, and pharmacological effect.

Different computational approaches are now used in nearly all areas of pharmaceutics. For example [1]:

1. Cyclodextrins: which are used in drug delivery of poorly solubilized drugs.

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2. Polymeric-based micellar vehicle: for delivery of hydrophilic and lipophilic drugs.
3. Biological lipid membrane: such as liposome in drug delivery for cancer.
4. Proteins and peptide drugs.
5. Inorganic nanoparticle: delivery of drugs and genes.
6. Physiology-based pharmacokinetics: preclinical drug development and formulation development.

14.2 History of computers in pharmaceutical research and development

Computers were not necessary for scientists or any manager of a company a few years ago, but now they can perform multiple complex jobs at once, such as transporting, storing, and organizing information, they are very necessary. With time, scientists discovered that there is a correlation between a molecule's chemical structure and its calculable molecular properties, which will enable the prediction of the molecule structure [3]. In World War II, a nuclear bomb simulation was one of the first uses of computers [1]. Pharmaceutical businesses started using computers in the 1940s, but they were only utilized for payroll and accounting, not for science [3]. Innovative studies tackled the issue of connecting electrical structure and biological activity in the 1950s. One of the pioneering contributions to computational drug research was made by Lilly in the early 1960s when they discussed the relationship between the estimated electrical structure of cephalosporins and their antibacterial activity. About all computational chemists worked in academia rather than industry in 1960. One segment of the industry consisted of students from such academic facilities, while another segment featured chemists trained in utilizing computers (X-ray crystallographers) for drug discovery. Drug development in the early 1960s was a trial-and-error process. Plants with medicinal characteristics and soil microbes were the two primary sources of therapeutic chemicals at that time [4]. A heated argument between computational and medicinal chemists was going on at the time. While medicinal chemists do not think it could work, computational chemists thought it was easier computationally to change a structure (to substitute atoms or add substituents) [5]. The prospect of computations on biomolecules and macromolecules was sparked by a book written in 1963 by Bernard and Alberte Pullman of Paris, France. A simplified mathematical representation of the function played by molecular descriptors in defining biological activity was developed in 1964 when the subject of quantitative structure−activity relationship (QSAR) was studied. The main source was classical medicinal chemistry. The chemists laboriously read books and patents while applying their creativity and expertise to produce therapeutically useful compounds, which were then screened by microbiologists and biochemists [6]. These traditional methods demanded time and

money, and they occasionally lacked accuracy. Abbott, Schering-Plough, Upjohn, and Dow Chemicals are among the companies that have taken the initiative in looking at the use of computers in drug research. When it discovered a connection between the estimated electronic structure of the beta-lactam ring in cephalosporins and their antibacterial activity, The Lilly Company produced the first significant development in computational drug discovery [7]. Following the IBM 360 model, the 370 series was released, and at that time, input devices gradually changed from punch cards to dumb terminals. For molecular mechanics, the well-known MMPI program was still in use, and FORTRAN software was still used. Then, the pharmaceutical industry began transition from using only quantum physics to using molecular mechanics, QSAR, and statistics [8]. But in the background, a conflict broke out between computational and medicinal chemists. Lilly initiated communication between the two teams and organized a number of workshops where medicinal chemists could learn how to calculate molecules using computational methods. Merck substituted a comparable workshop in its place [9]. Two databases—the Protein Databank (PDB) and the Cambridge Structural Database (CSD) were created in the early 1970s [10]. This provided computational chemists with more medicinal compounds to study [11]. In 1984 the Apple Macintosh made its debut, providing tiny laboratories with word processing, graphics, and database administration. This synthetic medicinal chemist has begun to value computational methods [12]. Professor Allinger established the Journal of Computational Chemistry in the 1980s [13]. There were three advancements during this time. First, the development in communication has made it possible for computers to interact with one another and with huge databases. Second, the creation of tools like ChemDraw in software. Thirdly, using a ball and stick or space-filling model, it is possible to explore the compound in its 3D structure. With all of these developments, an increasing number of businesses adopt the computer-aided molecular design process [14]. Computers first appeared in scientific breakthroughs around the middle of the 19th century. In order to anticipate biological activity, it is utilized to discover QSAR, which is a statistical investigation of a relationship between molecular structure and their descriptor [15]. From the mysterious IBM mainframes to the VAX computers, the computational chemists moved their computer programs. Merck released their system in 1980 after growing their modeling division into one of the largest in the world. For molecular modeling, 25% of the 48 companies used SYBYL from Tripos Associates, while 15% used CHEMGRAF from Chemical Design Ltd. MDL, a leader in the field of chemical structure management at the time and based in Hayward, California, provided a program called MACCS for handling databases of data on synthetic compounds [16]. X-PLOR, a program for data refinement that includes a force field, was inspired by CHARMM in the 1980s [17]. The Floating-Point System (FPS) had been purchased by several pharmaceutical businesses. An effective technique for precisely determining the binding energy between ligands and macromolecular targets is the free energy perturbation (FEP) hypothesis [18]. During this time, the idea that

computations constituted the "third way" of science was occasionally heard. Supercomputers started to appear in the 1990s, which increased the importance of computational drug discovery [19]. So, what a computer can do [20]:

1. Identify if the new compound can bind and fit to the protein receptor.
2. Predicts possible side effects which is a very substantial when known as early as possible to reduce the cost and time.
3. Identify drug candidate that can bind to different receptors in the body at the same time for better treatment of a certain condition.

For molecular modeling and simulations, programs like SYBYL (Tripos), Insight/Discover (BIOSYM), and Quanta/CHARMm (Polygen, subsequently Molecular Simulations Inc., and now Accelrys) were well-liked worldwide [21]. The California business known as BioDesign later changed its name to Molecular Simulations Inc. (MSI). Merck developed a force field from scratch, which they refer to as the Merck Molecular Force Field (MMFF94). ISIS (Integrated Scientific Information System), a new version of MDL's compound management software, was released in 1991. Researchers were given amazing new tools for drug discovery via MACCS and then ISIS. Although docking technology has been around since the 1980s, it became increasingly common for crystal structures of pharmaceutically important proteins to be solved and used for ligand design in the 1990s. Around 1993, combinatorial chemistry approach was executed wherein a library of compounds can be synthesized at a time. A chemist might easily manufacture 2000 compounds each week with combi-chem [22]. Combi-chem and high-throughput screening (HTS) created a lot of data, which required management and analysis. Consequently, the importance of computers and the study of informatics increased. Pharmaceutical businesses' intranets are set up with assistance from computational chemists and information technology (IT) experts. The hardware condition kept changing. Speed, random-access memory (RAM) capacity, and hard drive size of personal computers all increased [23]. The now-famous "Rule of Five" by Lipinski was first presented in 1997 and was quickly embedded in database mining operations at every business. The phrase "computer-aided drug design" (CADD) was coined, and the Lilly Company began compiling its successes in 1997 [24]. The medications that were discovered using CADD technology are shown in Table 14.1.

14.3 Statistical modeling in pharmaceutical research and development

Major challenge for the pharmaceutical industry in drug discovery and development: Reduction of costs and time from discovery to market. The process of discovery and development of new drugs has been drawn to highlight the pivotal role that models (simplified mathematical descriptions of real-life mechanisms)

Table 14.1 Drugs discovered through computer-aided drug design (CADD) technology.

Generic name	Brand name	Year approved in the United States	Discovery assisted by	Activity
Norfloxacin	Noroxin	1983	QSAR	Antibacterial
Losartan	Cozaar	1994	CADD	Antihypertensive
Dorzolamide	Trusopt	1995	CADD/SBDD	Antiglaucoma
Ritonavir	Norvir	1996	CADD	Antiviral
Indinavir	Crixivan	1996	CADD	Antiviral
Donepezil	Aricept	1997	QSAR	Anti-Alzheimer's
Zolmitriptan	Zomig	1997	CADD	Antimigraine
Nelfinavir	Viracept	1997	SBDD	Antiviral
Amprenavir	Agenerase	1999	SBDD	Antiviral
Zanamivir	Relenza	1999	SBDD	Antiviral
Oseltamivir	Tamiflu	1999	SBDD	Antiviral
Lopinavir	Aluviran	2000	SBDD	Antiviral
Imatinib	Gleevec	2001	SBDD	Antineoplastic
Erlotinib	Tarceva	2004	SBDD	Antineoplastic
Ximelagatran	Exanta	2004	SBDD	Anticoagulant

play in many R&D activities. Statistical models are used to know and predict the efficacy of a drug for a specific individual. This is done by recognizing the group of people who responds well to the drug tested and show no or minimal side effects, as people respond differently to a certain drug due to interindividual variation. The data obtained from this study is undergone a statistical analysis to predict the drug efficacy [25]. The typical and standard way to discover a new drug is by trial and error, as it was mentioned earlier, which is expensive and time consuming. The development of the pharmaceutical models, which improves the quality, reduces the cost and the time needed to discover a new drug, was a breakthrough [26]. Modeling concept is used to translate the already known properties about some hypothesis into a mathematical representation to simplify the data represented. The goal of statistical modeling is to develop a system, which can predict the response to the variables input in the future, elicit information about the connection between input variables and the need to response variables, and fully understand the mechanism that created the data or going to create this data. Descriptive modeling is used if the aim is only to obtain rational data without the need to understand the main phenomenon and this is beneficial in distinguishing between alternative assumptions. Mechanistic modeling's aim is to understand the mechanism of action, and this is done through cooperation between scientists, field specialists, and mathematicians or statisticians, by translating the scientific information into a mathematical model. The research areas of pharmacokinetics/pharmacodynamics (PK/PD) models are built to characterize

the kinetics and action of new compounds, designing new experiments and optimizing drug dosage. Models are also developed in other areas, like medicinal chemistry with QSAR-related models. These can all be defined as mechanistic models and are very useful. But in these models, the stochastic noise inherent in the data, the variability that makes biology different from physical sciences, is not as a general rule appropriately taken into account. Hence, many models of a different type are currently used in the biological sciences. These can be envisaged as complicated (mathematical) extensions of ways to analyze results. This is the area currently occupied by most statisticians. Using empirical models, universally applicable, whose basic purpose is to appropriately represent the noise, but not the biology or the chemistry, statisticians give whenever possible a denoised picture of the results. In clinical trials, the statistician is consulted up front to help in designing the experiment, to ensure that the necessary denoising process. This is the area of empirical models. The dividing line between empirical models and mechanistic models is not clear. Mechanistic models are usually based on chemical or biological knowledge.

These models are considered as interpretable or meaningful, but their inherent nature (nonlinearity, high number of parameters) poses other challenges, particularly once several sources of noise are also to be adequately modeled. For these reasons, empirical approaches have been largely preferred in the past. Today, however, the combination of mathematics, statistics, and computing is widely used. The way to optimally conceive an experiment depends on the a priori model you have. If you have very little a priori usable information (i.e., a poor model), then you will need many experiments and samples, making your practice not very cost effective. This is a bonus few realize from having models supporting the cycle: the cost, speed, and effectiveness. Modeling is the keystone to installing a virtuous cycle in the pharmaceutical industry, in order to successfully overcome approaching hurdles. There are two cultures (data modeling culture and algorithmic modeling culture) in the use of statistical modeling to reach conclusions from data. Data modeling culture assumes that the data are generated by a given stochastic data model, while algorithmic modeling culture uses algorithmic models and treats the data mechanism as unknown.

14.4 Computational modeling of drug disposition

The number of potential drugs that are being synthesized in recent years has increased markedly. These drugs may be not effective, have poor target binding due to poor absorption, inappropriate distribution, or rapid metabolism. The drug discovery has focused on efficacy and selectivity against the biological target.

As a result, almost half of the medication candidates in phase II and phase III clinical trials are unsuccessful due to unfavorable drug pharmacokinetics characteristics, such as unsatisfactory drug absorption, distribution, metabolism, excretion,

and toxicity (ADMET). In order to cut costs, early in the drug discovery process, in vitro evaluation of ADMET characteristics has become popular. In order to replicate membrane permeability and estimate in vivo absorption, Caco-2, and Madin-Darby Canine Kidney (MDCK) cell monolayers are frequently utilized. So, it is essential to screen their ADME characteristics to ensure the drug is effective and safe. Screening ADME in vitro is not cost-effective and cannot meet the increasing number of new drugs. Because of these in vitro findings, in silico models can now be trained and used to predict the ADMET characteristics of drugs even before they are ever manufactured. There have been significant developments in in silico modeling algorithms and a proliferation of computational programs that model drug ADMET characteristics. This urged pharmaceutical companies to investigate in silico prediction of pharmacokinetics data [27]. A number of commercial ADMET modeling programs were released and gathered (Table 14.2).

Simulation models have succeeded to predict [28]:

1. Extent and rate of absorption
2. Plasma concentration-time profile
3. Metabolic stability
4. Volume of distribution
5. Effect of drug−drug interactions

The tools that are available to predict ADME are filters, models, and simulations. Filters are a set of rules that are useful at very early stages (building of virtual libraries). Models are employed for the lead optimization to reduce the

Table 14.2 List of commercial absorption, distribution, metabolism, excretion, and toxicity (ADMET) modeling softwares.

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
QikProp	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

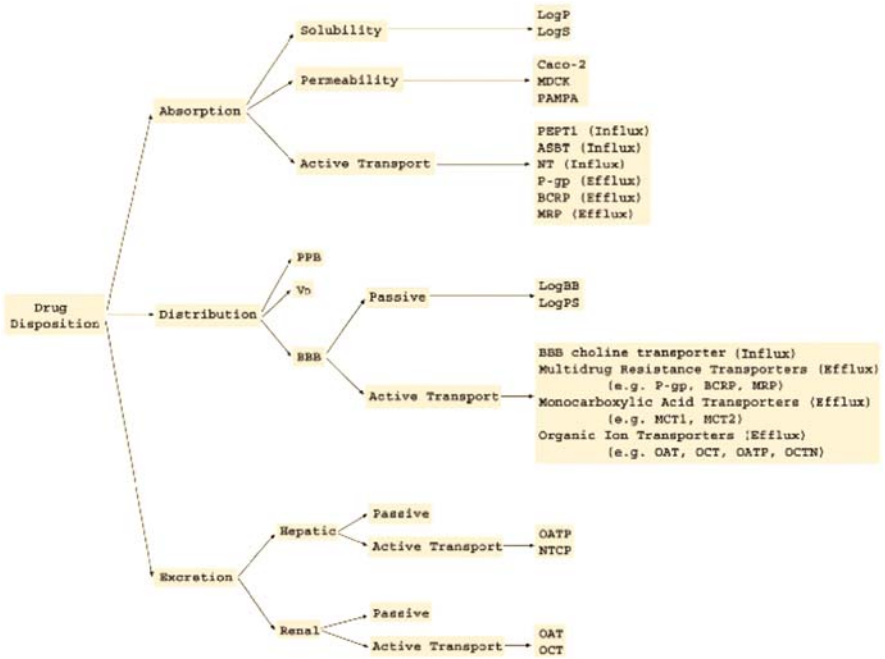

FIGURE 14.1

In silico modeling targets of drug disposition.

number of candidates. Simulation is useful in the selection of clinical candidates [29]. Fig. 14.1 describes in silico modeling targets of drug disposition.

QSAR and quantitative structure−property relationship (QSPR) research provides qualitative strategies that use multivariate analysis to link molecular descriptors with ADMET-related features. A wide selection of statistical algorithms is available to researchers for correlating field descriptors with ADMET properties including simple multiple linear regression (MLR), multivariate partial least-squares (PLS), and the nonlinear regression-type algorithms such as artificial neural networks (ANN) and support vector machine (SVM). Just like descriptor selection, it is essential to select the right mathematical tool for the most effective ADMET modeling. Sometimes it is necessary to apply multiple statistical methods and compare the results [30].

14.4.1 Absorption

Because of its convenience and good patient compliance, the oral route of administration is the most preferred drug delivery form. Thus, greater attention toward in silico approaches is aimed at modeling drug oral absorption, which mainly occurs in the human intestine. The drug bioavailability and absorption are the

result of the interplay between drug solubility and intestinal permeability. A drug generally must dissolve before it can be absorbed from the intestinal lumen. Direct measurement of solubility is time-consuming and requires a large amount of (expensive) compound at the milligram scale. By measuring a drug's logP value (log of the partition coefficient of the compound between water and *n*-octanol) and its melting point, one could indirectly estimate solubility using the "general solubility equation." For the prediction of the solubility of the compound even before synthesizing it, in silico modeling can be implemented. There are mainly two approaches to modeling solubility. One is based on the underlying physiological processes, and the other is an empirical approach. The dissolution process involves the breaking up of the solute from its crystal lattice and the association of the solute with solvent molecules. For drug-like molecules, solvent−solute interaction has been the major determinant of solubility and its prediction attracts the most efforts. LogP is the simplest estimation of solvent−solute interaction and can be readily predicted with commercial programs such as CLogP, which utilizes a fragment-based approach. Empirical approaches, represented by QSPR, utilize multivariate analyses to identify correlations between molecular descriptors and solubility [31].

Intestinal permeation describes the ability of drugs to cross the intestinal mucosa separating the gut lumen from the portal circulation. It is a process for drugs to pass the intestinal membrane before entering the systemic circulation to reach their target site of action. The current models aim to simulate in vitro membrane permeation of Caco-2, MDCK, or PAMPA (parallel artificial membrane permeability assay) which have been a useful indicator of in vivo drug absorption. Caco-2 is an immortalized cell line of human colorectal adenocarcinoma cells. It is primarily used as a model of the intestinal epithelial barrier. MDCK cells are a model mammalian cell line used in biomedical research. The PAMPA is used as an in vitro model of passive, transcellular permeation. The process involves both passive diffusion and active transport. The ionization state will affect both solubility and permeability. The ionization constant value (pKa) indicates the strength of an acid or a base [32].

Intestinal epithelial cells include influx and efflux transporters, which can either increase or decrease oral absorption. Drugs that mimic their native substrates are actively transported across the epithelial cell by flux transporters like the human peptide transporter 1 (hPEPT1), apical sodium bile acid transporter (ASBT), and nucleoside transporters. Drugs that have been ingested are actively pumped back into the intestinal lumen by efflux transporters such as P-glycoprotein (P-gp), multidrug resistance-associated protein (MRP), and breast cancer resistance protein (BCRP). To correctly predict overall oral absorption, drug metabolism in intestinal epithelial cells by cytochrome P_{450} enzymes should also be considered [33].

Advantage of in silico model to predict absorption:

1. It has a good capability of modeling saturable transporter and enzymes.
2. It can simulate the fraction of drug metabolized.

3. It can retain appropriate plasma concentration—time kinetics can be generated that consider the change in both time and dose.

The disadvantage of these programs is that the input required (dose, dosage form, logP, pKa, molecular weight) may limit their use as these inputs may not be generated [34]. The target property for most models is the logarithm of solubility (logS), and many models are trained and verified with the AQUASOL (http://www.pharmacy.arizona.edu/outreach/aquasol/) and PhysProp (http://www.syrres.com/esc/physprop.htm) databases. Softwares to predict intestinal permeation are SCSpKa (ChemSilico, Tewksbury, MA), Pallas/pKalc (CompuDrug, Sedona, AZ), ACD/pKa (ACD, Toronto, ON, Canada), and SPARC online calculator. Much software for simulating the ADME process has been produced. This includes GastroPlus, DEA pKEXPRESS, PK-Sim, and Cloe PK. GastroPlus and iDEA programs are useful in modeling of the absorption process by considering solubility and permeability. In a more developed version, the effect of P-glycoprotein interaction and CYP3A4 metabolism is considered [35].

14.4.2 Distribution

Distribution is an important aspect of a drug's pharmacokinetics. The structural and physiochemical properties contribute to the drug's distribution governed majorly by three important parameters: volume of distribution (VD), plasma-protein binding (PPB), and blood−brain barrier (BBB) permeability. VD is a measure of the relative partitioning of drug between plasma and tissue, an important proportional constant that, when combined with drug clearance, could be used to predict drug half-life and is a major determinant of how often the drug should be administered. BBB maintains the restricted extracellular environment in the central nervous system (CNS). For drugs that target the CNS, it is imperative that they cross the BBB to reach their targets. For drugs with peripheral targets, it is desirable to restrict their passage through the BBB to avoid CNS side effects. Most approaches model log blood/brain (logBB), which is a measurement of the drug partitioning between blood and brain tissue. Three types of drug efflux transporters of the brain are multidrug resistance transporters, monocarboxylic acid transporters, and organic ion transporters. Tools are also available to predict tissue distribution using physicochemical properties [36].

14.4.3 Metabolism and excretion

The prediction of metabolism is the most challenging aspect of drug's pharmacokinetics. METEOR and META are the available programs for metabolite identification to provide crucial early warns of potential toxicity. We can predict the site of metabolism within molecule and likelihood of metabolism. This is also beneficial because studying metabolism in animals may not reflect the actual metabolism in humans due to species differences in metabolism [34]. The excretion or

clearance of a drug is quantified by plasma clearance, which is defined as plasma volume that has been cleared completely free of drug per unit of time. Together with VD, it can assist in the calculation of drug half-life, thus determining dosage regime. Hepatic and renal clearances are the two main components of plasma clearance. Current modeling efforts are mainly focused on estimating in vivo clearance from in vitro data.

14.4.4 Transporters in absorption, distribution, metabolism, excretion, and toxicity

Given the prevalence of transporters on barrier membranes and the wide overlap between the substrates of transporters and many medicines, transporters should be a fundamental component of any ADMET modeling tool. The study of transporters has produced a sizable amount of in vitro data, which in turn has made it possible to create pharmacophore and QSAR models for many of them. Their incorporation into current modeling programs would also result in a more accurate prediction of drug disposition behavior [37].

14.4.4.1 P-glycoprotein

It is an efflux transporter that transfers a variety of substrates out of the cell in an ATP-dependent manner. By lowering absorption and boosting renal and hepatic elimination, it alters how drugs are disposed. P-gp is known to hinder the CNS penetration of human immunodeficiency virus (HIV) protease inhibitors and the intestinal absorption of the anticancer medication paclitaxel [38].

14.4.4.2 Breast cancer resistance protein

It is an additional ATP-dependent efflux transporter that provides resistance to certain anticancer medications. In addition to being highly expressed in solid tumors and hematological malignancies, BCRP is also found in the colon, liver, and brain, suggesting a complex involvement in drug disposition behavior. The model underlines the importance of extremely particular structural features for BCRP, such as a 2,3-double bond in ring C and a hydroxylation at position 5. In fact, this caveat should be considered for all predictive in silico models, because no model can cover all possible chemical space [39].

14.4.4.3 Nucleoside transporters

Both naturally occurring nucleosides and synthesized nucleoside analogs, such as cladribine, which are utilized as antiviral and anticancer medications, are transported by nucleoside transporters (e.g., zalcitabine). Nucleoside transporters come in a variety of forms, with each having a unique substrate specificity. Examples include concentrative nucleoside transporters (CNT1, CNT2, CNT3) and equilibrate nucleoside transporters (ENT1, ENT2). The high-affinity, selective CNTs are mostly found in the epithelia of the colon, kidney, liver, and brain, whereas

the broad-affinity, low-selective ENTs are found everywhere. One hydrogen bond acceptor and two hydrophobic components make up the pentose ring. The individual models also reveal the subtle characteristic requirements for each specific transporter. The modeling results also support the previous observation that CNT2 exhibits substrate-selectivity, whereas ENT1 shows substrate-specificity [40].

14.4.4.4 The human peptide transporter

The substrates such as β-lactam antibiotics and angiotensin-converting enzyme (ACE) inhibitors are transported through the low-affinity, high-capacity oligopeptide transport system. It has a major impact on drug absorption and excretion because it is mostly expressed in the intestine and kidneys. Following that, the CMC database with over 8000 drug-like compounds was screened using the pharmacophore model. The model recommended the HMG-CoA reductase inhibitor fluvastatin and the antidiabetic repaglinide [41].

14.4.4.5 The human apical sodium-dependent bile acid transporter

It is a very effective, high-capacity transporter that is expressed on the apical membrane of cholangiocytes and intestinal epithelial cells. It offers an alternative intestinal target for enhancing medication absorption by facilitating the absorption of bile acids and their analogs. One hydrogen bond donor, one negative charge, one hydrogen bond acceptor, and three hydrophobic centers were identified as being necessary for ASBT transport by the model. These requirements are in good agreement with a previous 3D-QSAR model derived from the structure and activity of 30 ASBT inhibitors and substrates [42].

14.4.4.6 The organic cation transporters

The organic cation transporters (OCTs) make it easier for many cationic medications to traverse various intestinal, liver, and kidney barrier membranes. The chemical class of organic cation (bearing a net positive charge at physiological pH) includes a wide variety of medications or their metabolites, such as antiarrhythmics, -adrenoreceptor blockers, antihistamines, antiviral medications, and skeletal muscle relaxants. OCT1, OCT2, and OCT3 are the three OCTs that have been cloned from different animals. By examining the degree to which 22 different compounds inhibited TEA uptake in HeLa cells, a human OCT1 pharmacophore model was created. The model implies that three hydrophobic properties and one positively ionizable feature are necessary for human OCT1 to be transported. Both 2D- and 3D-QSAR analyses were performed to identify and discriminate the binding requirements of the two orthologs [43].

14.4.4.7 The organic anion transporters

By actively transporting them across a wide range of tissue membranes, including those in the liver, colon, lung, and brain, it affects the plasma concentration of numerous medications. Organic anion transporters (OATPs) transport organic cationic medications as well as organic anionic pharmaceuticals, contrary to what

was once believed because of their broad substrate specificity. There are currently 11 human OATPs known, and most recently, a metapharmacophore technique was used to successfully predict the substrate binding requirements of the best studied OATP1B1. The metapharmacophore model revealed three hydrophobic features flanked by two hydrogen bond acceptor features as being the crucial requirement for OATP1B1 transport after analyzing a training set of 18 different compounds [44].

14.4.4.8 Blood–brain barrier-choline transporter

Choline, a charged cation, is transported into the CNS by the native nutrition transporter known as BBB-choline transporter. Because of its active transport, it helps choline-like molecules penetrate the BBB. Knowing its structural needs could help forecast BBB permeability more accurately. Geldenhuys and colleagues studied the requirements of binding of BBB-choline transporter using a combination of theoretical and empirical approaches, despite the fact that the BBB-choline transporter has not yet been cloned. The 3D-QSAR models were constructed with empirical K_i data determined using rat brain perfusion study involving structurally diverse compounds. Around the positively charged ammonium moiety, three hydrophobic contacts and one hydrogen bonding interaction were found to be crucial for BBB-choline transporter identification. It does provide a useful estimation of BBB-choline transporter binding requirements. More accurate in silico models could be generated once higher-quality data from the cloned BBB-choline transporter are available [45].

14.5 Computer simulation in pharmacokinetics and pharmacodynamics

The use of computer modeling for the pharmacokinetics and pharmacodynamic properties of the drug helped in developing the dosage form more rapidly, less expensive, and with less labor [46]. With the main goal of producing a drug that is nontoxic and effective [26] by a routine use of computer simulation in the course of drug development processes [27]. As the quality of data input increases, the chance of successful computer simulation of pharmacokinetic and pharmacodynamic increases, and by using the preceding studies as a reference to predict the computer simulation and so indicate the pharmacokinetic and pharmacodynamic parameters of each drug [46]. Some known famous agencies have already started to use computer simulation such as:

- Food and Drug Administration (FDA): They introduced a modern improvement in computer simulation modeling in the development process.
- US Environment Protection agency (EPA): It is becoming more conscious about the benefits of using the computational presentation of complicated systems to predict the behavior of the system or shrink the number of possibilities.

By mathematical representation of an organism, a lot of possibilities, which can be put under implementation (such as clinical trials simulation), can be investigated. Fig. 14.2 shows the map of exposure to response same as in clinical trials computer simulation.

The simulation of whole organism can be presented by:

1. Lumped parameter pharmacokinetic pharmacodynamic models: The reason for this study is to identify the pharmacokinetic and pharmacodynamic properties and also to predict the dosage regimen of the population by modeling analysis. The plasma concentration versus time using two two-compartment linear models and body weight related to central volume distribution is used to predict the behavior overtime but frequently the prediction occurs by nonlinear models to evaluate the parameter values of the population and their statistical distribution.
2. Physiological modeling (physiological-based pharmacokinetic model): PBPK uses the usual differential equations describing the interacting organs and organisms in more details by increasing the number of these equations.

The simulation of isolated tissue and organs, such as the kidney, brain, heart, and liver, are handled by mathematical modeling research. The heart and liver were massively investigated, and the heart and liver computational simulations were done by distributed blood tissue exchange models (BTEX). The incorporation of organ modeling with whole organism modeling will lead to a better result of PBPK [47]. Importantly, the currently available transporter models only cover a small fraction of all transporters involved in drug disposition. Other than incorporating current stand-alone transporter models into systemic models to directly predict drug pharmacokinetic properties, continued efforts are still needed to investigate other transporters such as MRP, BCRP, NTCP, and OAT, to get a more complete understanding of the drug pharmacokinetic profile. Not all pharmaceutical companies can afford the resources to generate their own *in-house* modeling programs, so commercial in silico modeling becomes an attractive option.

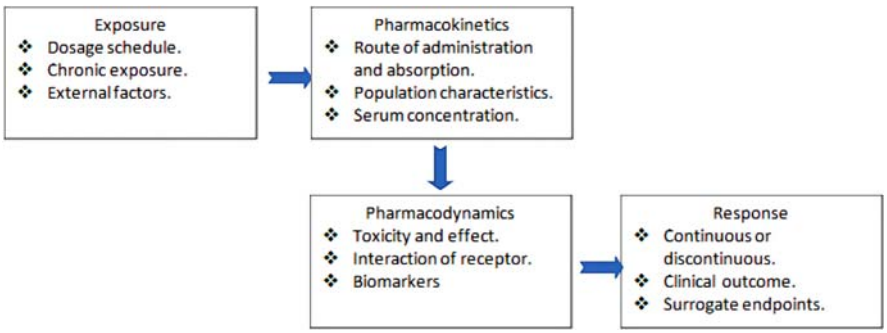

FIGURE 14.2

Map of exposure to response.

14.6 Artificial intelligence in pharmaceutics

AI is the simulation of tasks, such as language understanding, planning, and problem-solving, that require human intelligence. A system based on technology called AI can replicate human intelligence by using a variety of cutting-edge tools and networks. AI employs hardware and software that can comprehend and gain knowledge from input data in order to make independent decisions for the accomplishment of predetermined goals. A number of approach domains, including machine learning (ML), knowledge representation, and reasoning, are involved in AI (ML). Artificial neural networks (ANNs) are utilized in the deep learning (DL) discipline of machine learning [48]. The development of pharmaceutical products is a highly specialized task that requires a lot of time and experience [49]. Stepwise development is presented in Fig. 14.3 and classification is presented in Fig. 14.4.

So, the use of AI can result in better quality and productivity as well as shorten the development time [2]. We can exploit the powers of computers and pharmacists to achieve a better outcome. These comprise of sophisticated set of integrated computing elements involving "perceptons" analogous to human neurons, representing the signal transmission of electrical impulses inside the human brain.

14.6.1 Expert system

There are two technical approaches of AI: expert systems and machine learning [47]. Expert system is an obvious programmed rule. The expert system analyzes the characteristics of active pharmaceutical ingredients and recommends the one with accepted characteristics. It has many applications in pharmaceutics, for example, it is used to predict the drug release from osmotic tablet, design of oral

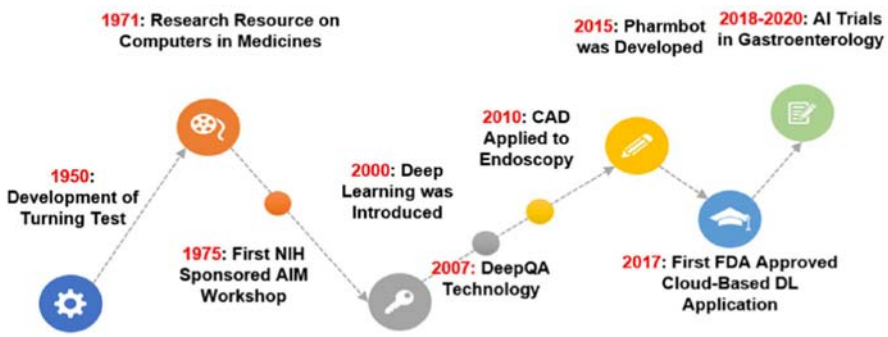

FIGURE 14.3

Stepwise development of artificial intelligence (AI).

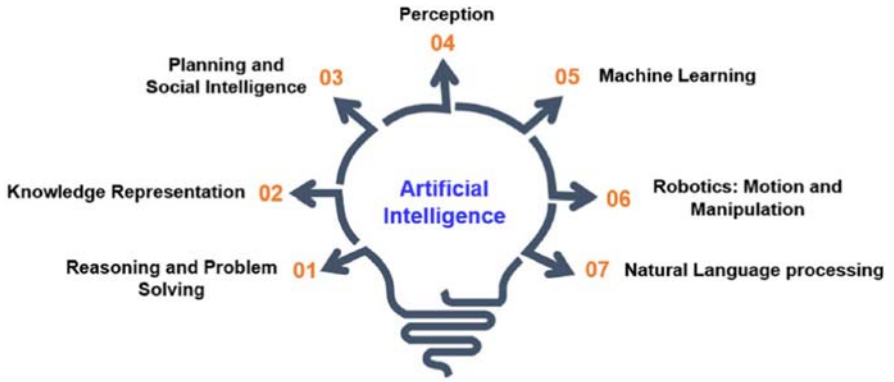

FIGURE 14.4

Classification of artificial intelligence (AI).

disintegrating tablet, and drug-excipient compatibility research. Machine learning is a mathematical approach that is highly useful when there are no specific rules to regulate a particular phenomenon [47].

14.6.2 Machine learning

Machine learning can be used in many fields of pharmaceutics: (1) to predict the performance of various dosage forms; (2) to predict physical stability and solid dispersion; (3) to investigate the dissolution behavior of solid dispersion; (4) to predict the nanocrystal that is used in drug delivery system; (5) construct a model to decide what to use oil, surfactant, or cosurfactant to form self-microemulsifying drug delivery system (SEDDS) [2]. AI could be used in drug delivery systems to study the ADME profile by simulating the human body environment which allows us to research and investigate multilayered data [48]. AI can gather data from multiple sources to give us a clue whether the drug could suit the drug delivery system or not by evaluating the pharmacokinetics and patient information. Examples of applications of AI in pharmacy are:

1. To predict the structure of proteins by AlphaFold 2 which is produced by google's deep-mind.
2. To predict the drug release parameter by ANNs which manifest a high accuracy.
3. To predict the best treatment for a patient like insulin pump which contain AI algorithm to deliver the right dose of insulin.
4. To improve the nanotechnology delivery.

However, AI has disadvantages that limit their use like lacking data [49]. The implication of AI in drug discovery is presented in Fig. 14.5.

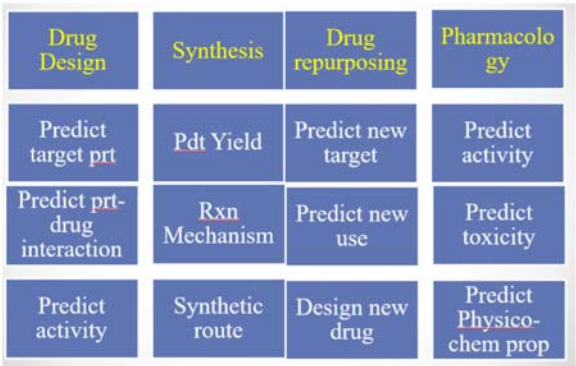

FIGURE 14.5

Artificial intelligence (AI) in drug discovery.

14.6.3 Challenges of artificial intelligence in drug discovery

Businesses that employ AI for drug research must go through a rigorous process to copyright their work in order to obtain patent rights. Because AI-driven tailored treatment involves a person's genetic code, security is another key worry (legal issues). Big data will require faster calculation, and it is predicted that quantum computers will eventually replace the current supercomputers. There is still no success story of an AI-generated substance reaching the market and being used by the general public. A biotechnology startup called In silico Medicine proposed a novel target involved in idiopathic pulmonary fibrosis and created its own inhibitor using AI-based technologies. The found small molecule inhibitor has demonstrated good efficacy, and the company submitted an investigational new drug (IND) application in December 2020. The anticipated clinical studies are scheduled to begin at the end of 2022.

14.7 Pharmaceutical automation

As the pharmaceutical industry is continuously developing through the evolution of newer technologies, the industry needs a new way to adapt to such development to get the maximum production, reduce the cost and the time, this can be done by pharmaceutical automation which means manufacturing automatically [50].

Automation is unavoidable as it shows a lot of improvements in performance in the pharmaceutical industry with many great advantages such as:

1. Accuracy: Remove human error and because it is automated and it does not require a learning curve to learn how to blend, weight, tableting of solids, stirring, and filling of liquid.
2. Effective: Automated machines can do tedious work at higher speed than humans and it can work 24 hours.

3. Lower contamination: As the humans work less in the handling and production of products, the contamination risk will decrease.
4. Clarity: Automation make it possible for end-to-end tracking of products by the final delivery, records the batch electronically, radio frequency identification, and performance management can help in identifying any ineffective products and fix them.
5. Return on investment: The advanced costs of automation technology can all be returned over that time because the automated machines will enhance quality, supply energy saving, and provide rapid production.

Pharmaceutical automation applications:

- Compression and coating of tablets.
- Dosing of liquids.
- Filling, packaging, and drug delivery systems.
- Tracking and the ability to trace.
- Encapsulation of liquid and solid dosage forms.
- Labeling of radio frequency identification.
- Different processes such as high-shear wet granulation, dry granulation, fluid bed granulation, milling, drying, extrusion, blending, and microionization [50].

The AI tools are employed in speeding up or facilitating the entire drug discovery process (Fig. 14.6).

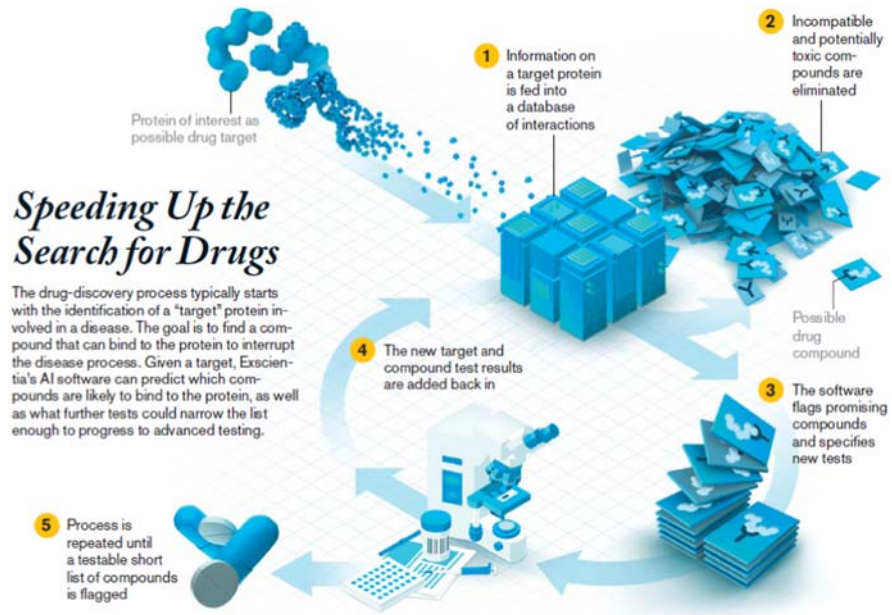

FIGURE 14.6

Artificial intelligence (AI) in facilitating the drug discovery process.

14.8 Conclusion

Increased attention has been recently focused on computational pharmaceutics as a useful method, for the effective development of new drug delivery systems to speed up the development process, save time and money, and modify the formula to get optimal delivery systems with good solubility, absorption, stability, and pharmacological effect. Computational pharmaceutics involves quantum mechanics, physiologically based pharmacokinetic modeling, simulation of molecular dynamics, process simulation, mathematical modeling, machine learning algorithms, and AI. These models can help in predicting the physicochemical properties of pharmaceutical formulations and examine the molecular mechanisms of molecular mechanics-based formulations; thus, improving therapeutic efficacy, reducing running costs, and saving time and energy.

Consent for publication

Not applicable.

Conflict of interest

The authors declare no conflict of interest, financial or otherwise.

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