CHAPTER

21

Computer-Aided Prediction of Pharmacokinetic (ADMET) Properties

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OUTLINE

Dosage Form Design Parameters
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21.1 INTRODUCTION

It is less frequent for drug manufacturers and researchers to pay much attention to the development of drugs having poor pharmacokinetic profiles, because the processes associated with both the development as well as the discovery of drugs are considered to be highly costly, which is economically inefficient in the perception of drug developers and researchers as well (Boobis et al., 2002). Recently, an observable increase has been reported regarding the application of new industrial and academic models that are being relied on the study of drug's pharmacokinetic properties including absorption, distribution, metabolism, excretion, and toxicity (ADMET) (Fig. 21.1) (Ekins et al., 2000). Limitations in the

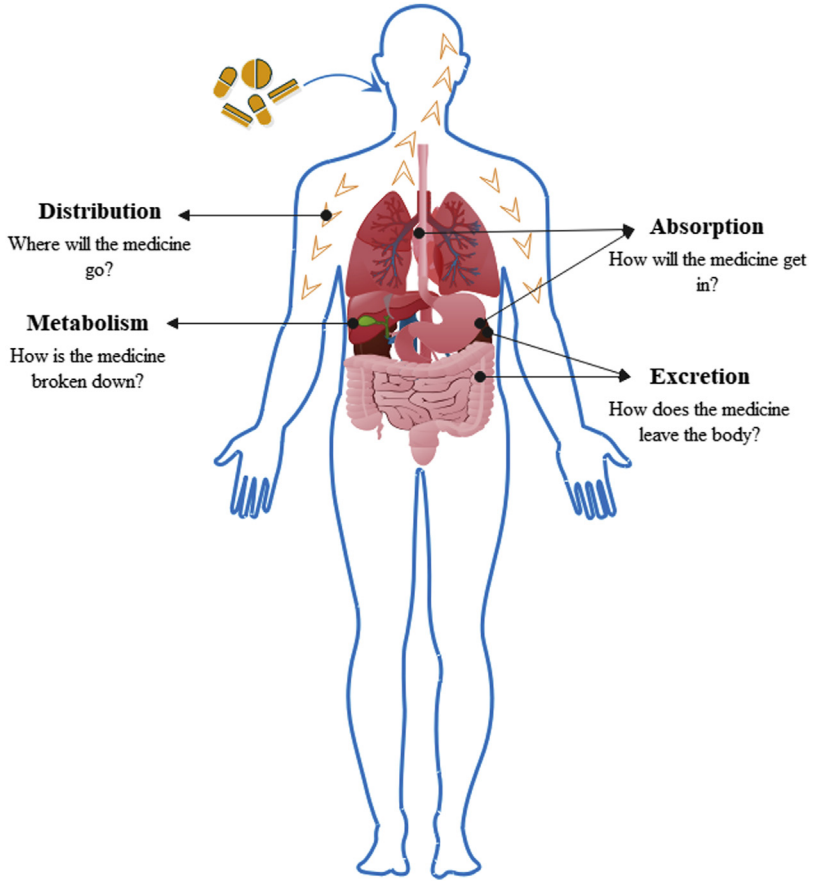

FIGURE 21.1 A scheme that represents a description of the ADME pharmacokinetic parameters of the drug and how these parameters affect the drug after oral administration.

development of new drugs were shown to be caused by the undesirable pharmacokinetic properties of these drugs, therefore, it has been increasingly demanded to evolve new approaches that are able to predict drugs' ADMET properties (Balakumar et al, 2017b; Butina et al., 2002; Mody et al., 2014; Tekade, 2014, 2015; Choudhury et al., 2016).

The development of ADMET prediction techniques took place in 1863, which was concerned with the traditional determination of the effect of drugs solubility on the toxicity. Later on, attention was paid for the study of ADMET more specifically, which started by measuring drugs aqueous solubility in addition to an *in vitro* testing (Dearden, 2007). A successful drug development has to involve respectable ADMET properties in addition to the good efficacy. The employment of new technologies in the prediction of drugs ADMET properties has taken drug development operations to a higher level. In the past early decades, computerized prediction techniques were shown to be applied along with *in vivo* as well as *in vitro* tests to facilitate drug discovery and development approaches (Moroy et al., 2012). *In silico* techniques have been introduced to the fields of development and discovery of drugs as a tool that predicts drug's ADME properties at the early stages (Boobis et al., 2002).

ADMET data is considered as an essential part of discovering and developing new drugs. Both *in vitro* as well as *in vivo* models provide parameters regarding drugs' ADMET properties, which in turn can be used to predict drugs' behavior after administration. ADMET parameters determine whether drug candidates are to be advanced, held, or terminated (Zhang et al., 2012). Preclinical data of drugs' ADMET properties play a role in the assessment of drugs targeting after administration since pharmacokinetic profiles can be estimated based on drugs ADMET data. Parameters including the absorption rate, the deposition, and the metabolism of the drug within the targeted organ are being taken into consideration when assessing drugs' exposure in the targeted site of action (Zhuang and Lu, 2016). In order to develop drugs with desired properties and optimal dosing regimens, it is very essential to determine the pharmacokinetic properties of these drugs, including their ADMET (Hop, 2012a,b). Due to various risk factors associated with the development and discovery of drugs along with the time-consuming processes involved, *in vivo* models were conducted to reduce the expected undesired properties of drugs in the preclinical stages before introducing them to the market (Bohnert and Prakash, 2012).

Nowadays, drug developers are facing serious challenges to develop more efficient as well as cost-effective drugs as compared to the existing therapies, therefore, a need to optimize physicochemical properties including their bioactivities and the ADMET properties as well have arisen in order to develop drugs with the least adverse effects (Peach et al., 2012). Other properties that are taken into account when predicting the behaviors of newly-developed drugs are related to the size of doses and their frequencies as well. These properties include drugs' bioavailability, oral absorption, clearance, volume of distribution, as well as the penetration through the blood−brain barrier (BBB) (van de Waterbeemd and Gifford, 2000). One of the most important properties that has to be well-optimized is the relative solubility of drug substances since both toxicity and drug design are significantly dependent on it. Various problems were shown to be associated with poorly soluble drugs, which were reported to cause serious uptake problems as well as problems during manufacturing and storage (Hewitt et al., 2009). The metabolic stability of drugs is also considered as a crucial issue that drug developers have to pay great

attention to because development process success or failure is greatly dependent on the metabolism profile of these drugs (Peach et al., 2012).

21.2 OVERVIEW OF THE DEVELOPMENT OF ADMET PREDICTION MODELS

There are various factors that should be taken into consideration when developing an *in silico* ADMET prediction model. The characteristics of the model to be developed depend mainly on the application purposes of the model, for example, the degree of prediction accuracy varies depending on the required prediction speed of the model. In general, the higher prediction accuracy the model possesses, the more time-consuming the model is, because of the more calculations required for the prediction process (Bergström, 2005). Thus, it is important to clearly define the application purposes of the model to be developed in order to adjust it accordingly. In general, simple models that are fast in calculations are employed at stages where a high number of molecules requires quick assessment of their ADMET properties, while at more advanced stages in the drug development process, models with a high degree of prediction accuracy are required for the assessment of the ADMET properties (Ekins et al., 2000). Another important factor is to decide whether the model will be specific for a certain project where usually similar molecules are present or whether it will be a global model that is used for the prediction of structurally diverse molecules. Based on the required characteristics of the model, the selection of a proper set of descriptors to be used in the model and which statistical methods to apply can be determined to fit the purpose of the model to be developed (Hop, 2012a,b).

21.2.1 Descriptors

Molecular descriptors can be defined as mathematical representations of molecules' properties that are generated by algorithms. The numerical values of molecular descriptors are used to quantitatively describe the physical and chemical information of the molecules. An example of molecular descriptors is the LogP which is a quantitative representation of the lipophilicity of the molecules, it is obtained by measuring the partitioning of the molecule between an aqueous phase and a lipophilic phase which consists usually of water/*n*-octanol. Molecular descriptors can be useful in performing similarity searches in molecular libraries, as they can find molecules with similar physical or chemical properties based on their similarity in the descriptors' values. The molecular descriptors are used in ADMET prediction models to correlate the structure−property relationship to help in predicting the ADMET properties of molecules based on their descriptors values (Khan and sylte, 2007).

The molecular descriptors that are used in ADMET models can be classified as being one-dimensional (1D), two-dimensional (2D), or three-dimensional (3D) descriptors based on the level of molecular representation required for calculating the descriptor. The 1D descriptors are the simplest type of molecular descriptors, these represent information that

are calculated from the molecular formula of the molecule, which includes the count and type of atoms in the molecule and the molecular weight.

The 2D descriptors are more complex than the 1D descriptors, usually, they represent molecular information regarding the size, shape, and electronic distribution in the molecule. Calculating the 2D descriptors depends mainly on the database size, and the calculation of parts of a molecule in which the data is missing could largely result in a false result.

The 3D descriptors describe mainly properties that are related to the 3D conformation of the molecule, such as the intramolecular hydrogen bonding. Examples of descriptors obtained from calculations involving the 3D structure of the molecules are the polar and nonpolar surface area (PSA and NPSA, respectively). More advanced calculation like quantum mechanics calculations can be used to obtain 3D descriptors that describe the valence electron distribution in the molecules (Bergström, 2005).

21.2.2 Datasets

The development of a successful ADMET prediction model requires an accurate dataset that is suitable for use in the model. The number of the compounds and the structural diversity in the datasets determines whether the model will be developed as a "local model," where it is used for the prediction for a relatively similar class of compounds, or it will be a "global model" that can be used for the prediction of a different classes of compounds. Local models are generally used during advanced stages in the drug development process, because these models are specific to a class of similar molecules. While the global model are beneficial for use when a high number of compounds are present such as in the initial stages of drug development (Norinder and Bergström, 2007).

21.2.3 Statistical Methods

There are several statistical methods that are usually used in the development of ADMET prediction models. In the simplest form, a single descriptor is used for the prediction of a process, but generally, several descriptors are used for enhancing the prediction accuracy. Usually, multivariate data analysis (MVA) is used in this approach which includes multiple linear regression analysis (MLR) and multiple nonlinear regression analysis (MNLR). The partial least square (PLS) method represents a more advanced approach and is generally applied when there is a high number of variables and few observations in the dataset. This method is usually used in the development of drug absorption predictions models. It is also utilized in the quantitative structure–property relationships (QSPRs) (Hou et al., 2009).

21.2.4 Model Validation

Before an ADMET prediction model is used, it is important to validate the prediction ability of the model. One method that is usually applied for the model validation purpose, is to intentionally not include a portion of the dataset in the model and to use it as a test for the validation of prediction ability of the model following the model development.

Another method is to use an external dataset for testing the predictability of the model, this will validate the ability of the model to predict external datasets that are not part of the development. One problem associated with the process of model validation, is the overfitting of the model. It is necessary to avoid overfitting of the model in order to obtain a model that has useful prediction ability and can be used for the prediction of ADMET properties of external molecules that are not included in the datasets used during the model development (Norinder and Bergström, 2007).

21.3 *IN SILICO* PREDICTION OF PHYSICOCHEMICAL AND PHARMACOKINETIC PROPERTIES

Increasing studies have been conducted to describe the relationship between the physicochemical properties and the biological behavior of drug therapies. Physicochemical properties of drugs are manipulated by optimizing the changes in the chemical structures and their effects on the behavior as well (Wenlock and Barton, 2013). The resultant effect of a certain administered drug is due to the molecular recognition between both the drug (ligand) and its target (site of action). The spatial rearrangement of the ligand's atoms and how they interact with the target are responsible for the pharmacological activity of the drug. Such interactions and the dynamics, energetics, and structure associated can be characterized by computational approaches of chemistry. There are a number of physicochemical properties on which the biological behavior of the drug depends, such properties include water solubility, partition coefficient (LogP), melting point (MP), boiling point (BP), as well as the bioconcentration factor (BCF). On the other hand, various pharmacokinetic properties are shown to be affected by these physicochemical properties, and these include the drug's bioavailability, transfer, permeability, and others (Zang et al., 2017). Indirectly, physicochemical properties of the drug were reported to have an impact on the interpretation of the drug's pharmacokinetic properties during the early stages of discovery. Therefore, the utilization of *in silico* computational tools has taken place to predict both the drugs' physicochemical properties and their effect on the drugs' behavior after administration. (Wenlock and Barton, 2013)

21.3.1 *In Silico* Prediction of Physicochemical Properties

21.3.1.1 Lipophilicity

Lipophilicity, most commonly referred to as the LogP, represents the ratio at equilibrium of the concentration of a compound between two phases, an oil and a liquid phase (Bohnert and Prakash, 2012). Lipophilicity is a physicochemical parameter that has to be widely taken into account when developing new drugs since it has been reported to have a significant influence on various pharmacokinetic properties such as the absorption, distribution, permeability, as well as the routes of drugs clearance (van de Waterbeemd and Gifford, 2000; Prajapati et al., 2009; Tekade et al., 2009a, b; Dwivedi et al., 2013). It has been increasingly demanded to develop drugs with high lipophilicity in order to fulfill the required selectivity and potency of drugs. Such demands have basically arisen as a result

of the lipid nature of biological targets. For example, neurotransmitter pathway targets, anatomical targets, and/or the intracellular targets necessitate the binding of agonists with a respectable lipophilic nature to achieve the desired action (Bergström et al., 2016).

On the other hand, suitable drug formulations have to reflect a good aqueous solubility as well as an acceptable degree of lipophilicity in order to assess the best oral absorption along with the required deposition and activity. Therefore, automatic computational measurements of aqueous solubility, lipophilicity, as well as the degree of ionization have been applied and integrated in the discovery stages of drugs (van de Waterbeemd and Gifford, 2000). Due to the observable importance of lipophilicity parameter and its role in understanding the pharmacokinetic properties of drug candidates, a persistent need for accurate and precise *in silico* models for the prediction of lipophilicity has arisen. More specifically, models that predict the log P have been used and noticed to facilitate the process of drug design which in turn has aided in the development of other prediction approaches based on multiple fragments and atoms (Wenlock and Barton, 2013).

21.3.1.2 Hydrogen Bonding

Hydrogen bonding is considered the driving factor that plays an obvious role in the partitioning of the biologically active compounds. Hydrogen bonding reflects the interaction between the H-bond (HB) acceptor target and the H-bond (HB) donor compound or vice versa (Schwöbel et al., 2011). Hydrogen bonding capacity of bioactive substances has been reported to have a role in the determination of these substances permeability across the biological membranes. Furthermore, it was proven that in order for a compound to cross a biological membrane, hydrogen bonds have to be broken with the drug's aqueous environment. Therefore, it is relatively unfavorable for a compound to make many hydrogen bonds since that would inversely affect the degree of permeability and the absorption as well (van de Waterbeemd and Gifford, 2000). Various studies have represented the relationship between hydrogen bonding and the quantitative structure−activity relationships (QSAR)-based models. Therefore, it has been possible to quantify the strength of hydrogen bonds, which in turn is considered as an essential step in the structure-based stage of drug design (Schwöbel et al., 2011; Balakumar et al., 2017a).

21.3.1.3 Solubility

Aqueous solubility is a fundamental property that is nearly involved in every stage of drug development due to its role in the determination of drug uptake, transfer, and elimination from the body (Balakin et al., 2006; Prajapati et al., 2009; Kurmi et al., 2010; Kayat et al., 2011). Intrinsic solubility can be defined as the drug's thermodynamic solubility at a pH value where the drug is found to be completely in the unionized form (Bergström et al., 2016). Drugs' efficiency is primarily dependent on their aqueous solubility, therefore, drugs with poor solubility or low dissolution rates will be eliminated before entering the blood circulation and hence without giving the required pharmacological activity (Balakin et al., 2006; Jain and Tekade, 2013; Ghanghoria et al., 2016; Soni et al., 2016). The number of poorly soluble drugs has increased recently, and problems of poor absorbability, food effects, and the lack of pharmacokinetic linearity have appeared as well (Kuentz and Imanidis, 2013). Sufficient solubility data have been shown to significantly facilitate the development of drugs. In some cases, it is difficult to find drugs with the proper solubility

profile, hence, possible computational approaches can be used to predict the solubility and improve the absorption of drugs as well (Lüder et al., 2007). The solubility of chemical compounds is influenced by two important factors, namely, the lipophilicity and the tightness of the crystalline structure, and it should be noted that both parameters are related to the solubility in an inverse relationship (Bohnert and Prakash, 2012).

Although the solubility as a parameter is not always considered as an ADMET property, however, it is proven as a key factor in the determination of a drug's oral absorption. In other words, compounds having poor solubility in the gut will have low permeability and hence bad absorption as a result. This has motivated scientists to pay much attention to the prediction of a drug's solubility as an important factor during the process of drug development in the last few years (Clark, 2005). Despite the significant role of the solubility during different stages of drug development, yet observable deficiencies are shown regarding the consistent and reliable data needed for the prediction on a drug's solubility (Wenlock and Barton, 2013).

Computational models for the prediction of solubility on the basis of the molecular structure are usually achieved by MVA, and such models include the PLS, ANN, SVR, as well as RF (Bergström et al., 2016). A recent *in silico* study has demonstrated a useful computational methodology that is capable of predicting how the solid-state of materials is affecting the solubility. It is expected that this method in addition to other methods working on the same principles of molecular and quantum mechanics will have more potential in the future, and are expected to provide predictions with more accuracy. These methodologies are also expected to accurately predict the properties of crystal lattice and how they impact the solubility and dissolution rate of drugs, accordingly (Bergström et al., 2016).

21.3.1.4 Permeability

Permeable drugs primarily cross biological barriers including the intestinal epithelial and the BBB by the mechanism of passive diffusion, where substances are transported by the effect of a concentration gradient. Basically, there are two types of passive diffusion, one is the paracellular transport while the other is the transcellular transport mechanism; other drugs are being transported by either the carrier-mediated or the P-pg mediated transport (Fig. 21.2) (Hou et al., 2006). Drug permeability is described by the hydrogen bonding parameter as mentioned in various studies, and the majority of results have shown that less importance is associated with hydrogen bond (HB) acceptor descriptors when predicting the permeability of the human intestinal epithelium (Refsgaard et al., 2005). Several *in silico* models were introduced to accurately predict drugs' membrane permeability according to their lipophilicity profiles, the molecular size, H-bonding capacity, and the PSA as well. *In silico* prediction models were shown to make the development of new drug candidates a less time-consuming process (Balimane et al., 2000).

21.3.2 *In Silico* Prediction of Drug Absorption

Gastrointestinal absorption of drug substances is considered to be a complex mechanism (Fig. 21.3) due to several factors that are classified mainly into the physiological

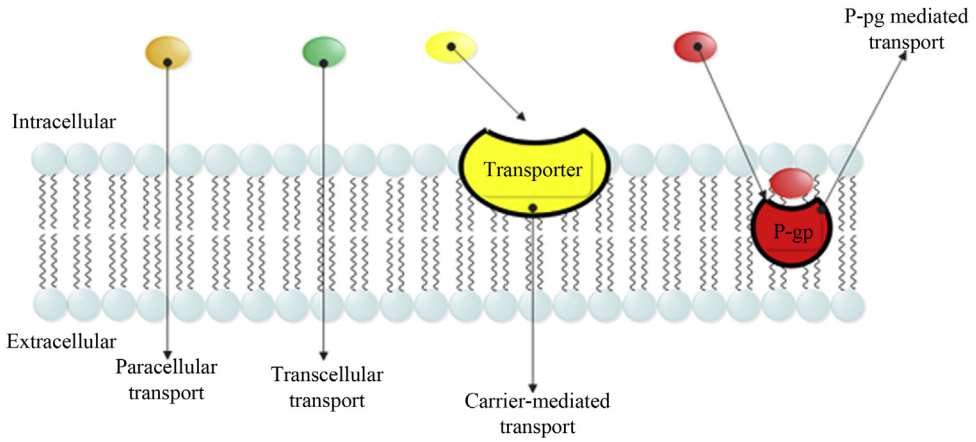

FIGURE 21.2 Schematic representation of the types of drug transport across the biological membranes including the paracellular and transcellular passive diffusion in addition to carrier-mediated and the P-gp-mediated transport.

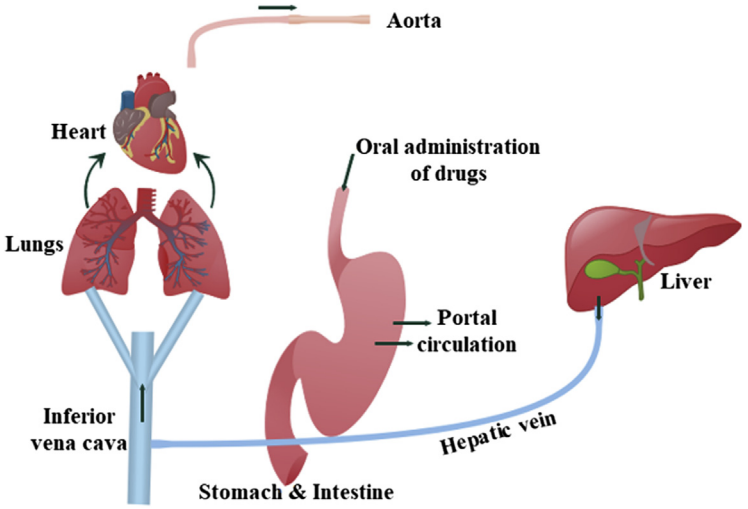

FIGURE 21.3 A scheme representing the complex mechanism associated with oral drug administration that involves the contribution of several body organs.

effects, the physicochemical effects, and the formulation effects (Fig. 21.4). Therefore, the prediction of drugs' absorption has been a major obstacle that used to face researchers and developers of drug candidates (Boobis et al., 2002). The absorption of orally administered drugs is basically characterized by one of three mechanisms that include the facilitated diffusion, the passive diffusion, and the active transport, depending on factors such as the particle size and the diffusion coefficient of the drug as well. Absorption can be

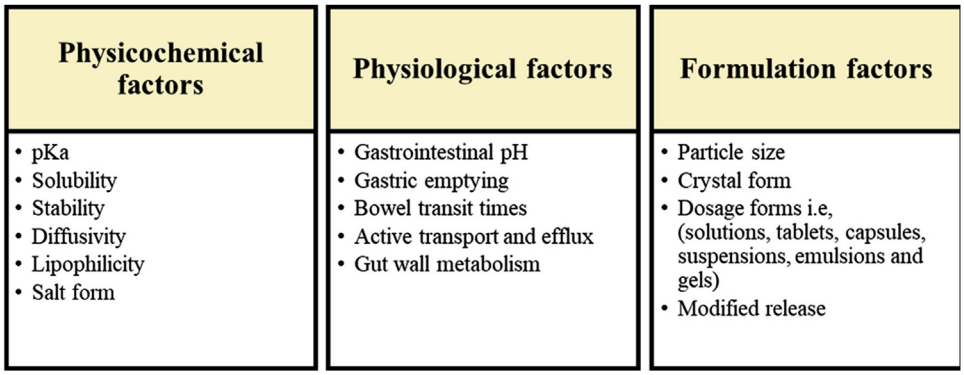

FIGURE 21.4 Major factors influencing the complexity of the absorption mechanism after a drug's oral administration, which include the physicochemical, physiological, and formulation factors.

determined by various techniques, and in some cases, it can be described in the terms of either the permeability or the solubility of the drug (Lamberti et al., 2016). There have been various *in silico* models for the prediction of oral absorption that were used along with models of *in vivo* and *in vitro* prediction technologies. *In silico* models have been applied to evaluate the influence of gastric pH on the exposure of drugs of weak bases, and in other cases, these models were used to predict the bioavailability, gastric acid function, and the risks associated (Saxena et al., 2015).

21.3.3 *In Silico* Prediction of Intestinal Permeation

Recently, several technologies have been introduced to the field of drug development, which in turn have resulted in a large number of drugs having unfavorable characteristics that include the higher lipophilicity, poor solubility, as well as the high molecular weight of these drugs as compared to the conventional ones. Thus, the improvement of prediction methodologies that are considered to be able to predict parameters, such as the intestinal permeability, has become a need. Generally, a sigmoidal relationship has been reported to be between the intestinal permeability and the lipophilicity of the drug substance, which means that the absorbability of a drug having a low molecular weight or not having a significant metabolism is usually governed by the intestinal permeability that is achieved by the mechanism of passive diffusion (Chaturvedi et al., 2001). Computational modeling techniques have provided the assessment of intestinal permeability of drugs under development before being synthesized by a procedure that is considered to be fast and inexpensive as well. Models including the basic models, the PSA, the fast PSA, in addition to other complex models are now used to predict the intestinal permeability—an essential part of drug discovery and development (Egan and Lauri, 2002).

21.3.4 *In Silico* Prediction of Drug Distribution

The pharmacokinetic profile of a drug substance is determined by various parameters including tissue distribution. Therefore, in order to accurately predict the *in vivo*

pharmacokinetic profile of a drug, the tissue distribution parameter has to be predicted during the drug development process. The prediction of tissue distribution has been also reported to facilitate the prediction of the pharmacodynamic properties and the toxicodynamics as well (Boobis et al., 2002). The prediction of drug distribution throughout the body is basically divided into three main areas of examination, which are the BBB permeability, the volume of distribution (VD), and the plasma protein binding (PPB). All of the three areas have an observable role in the determination of drug suitable regimens, the effective plasma concentration, and the permeability across the BBB, which in turn helps in predicting CNS targets, side effects, and non-CNS therapies as well (Lombardo et al., 2003). Nowadays, several methods are being used to predict drugs' tissue distribution, and the prediction can be achieved by examining either the volume of distribution of drugs at the steady state or the tissue:plasma ratios (Boobis et al., 2002).

21.3.4.1 In Silico Prediction of PPB

The PPB of drugs can affect both the pharmacokinetics and pharmacodynamics of drugs since generally, it is accepted that only the unbound (free) fraction of the drug is active, it is important to estimate the PPB of drug candidates. The most important protein involved in the binding with drugs in plasma is the human serum albumin, which can bind to a wide variety of endogenous and exogenous molecules. There have been various *in silico* models developed to predict the interaction of molecules with the human serum albumin. Many of these models are based on the available 3D crystal structures of albumin which can be utilized in performing docking studies to predict the binding of molecules with albumin (Moroy et al., 2012; Vallianatou et al., 2013; Balakumar et al., 2010). There have been also QSPR models developed based on the available data of various ligands that are known to bind to albumin (Ghafourian and Amin, 2013; Zhivkova and Doytchinova, 2012; Li et al., 2011). Other major proteins that also have the ability to bind with drugs in plasma are the alpha1-acid glycoprotein and lipoproteins, which have received less attention with regard to prediction models developed in comparison with the human serum albumin.

21.3.5 *In Silico* Prediction of Drug Metabolism

Drug metabolism has been recently estimated as one of the major parameters that has shown to be taken into serious consideration during the discovery, development, and design of drug candidates. Metabolic consideration has been integrated into the process of active drugs' development in order to make the development a less costly process that is not time-consuming. Various aspects of drugs' metabolism are being optimized during the early stages of development that include the chemistry, biochemistry, toxification and detoxification mechanisms, and metabolic interactions, in addition to the physicochemical properties and the changes associated with them (Testa et al., 2005). Some research reports stated that drugs' metabolism is the most difficult parameter to predict as compared to other pharmacokinetic parameters because the process of metabolism is a very complex process that involves various enzymatic activities that vary among individuals due to different genetic factors. Different computational (*in silico*) models were successfully applied to estimate relative predictions regarding the metabolism of some drugs.

A number of aspects are being optimized during the assessment of a drug's metabolism profile at the early stages, and these aspects include the metabolic routes, stability, and interactions along with the kinetics of metabolizing enzymes as well. These aspects were shown to be essential for the selection of the suitable drug candidates during the development and discovery of pharmaceutical drugs (Pelkonen et al., 2005). The cytochrome P450 (CYP) is considered to be the most influential enzyme in the drug metabolism, which led to the development of many models such as QSAR for the prediction of the metabolism of molecules by the CYP enzyme. These models are improving as more data regarding the CYP isoforms and ligands that bind to them are becoming more available, in addition to the data regarding the inhibitors of the enzyme, homology modeling of isoforms of this enzyme has also been useful in the development of prediction models. Another enzyme involved in the metabolism of drugs is the UGT enzyme, but in contrast with CYP, less advanced models are available for the prediction of the metabolism of molecules by this enzyme because of less data available regarding the substrates and isoforms of UGT (Khan and Sylte, 2007).

21.3.6 *In Silico* Prediction of Drug Excretion

Excretion refers to the process by which the body gets rid of the waste/toxic products. The drug excretion process can be achieved by either the kidney and/or the liver where drugs are eliminated in the form of urine or bile, respectively. The most important factor that determines the proper drug removal mechanism is the molecular weight, where substances of relatively small molecular weights are mainly removed through urine (Lamberti et al., 2016). Despite the fact that almost all drug substances are excreted out of the body, very little interest has been paid to the prediction of drugs' excretion parameters. However, since drugs of the second phase of metabolism usually exist in the unchanged form and hence the lack the pharmacodynamic activity, much considerable interest was observed regarding the prediction of phase metabolites excretion. Passive excretion can be predicted based on some approaches that include the flow rate, lipophilicity, protein binding, and the p*K*a value. After the prediction of a drug's excretion profile, collected information have to be integrated into a predictive model that provides a complete model describing the behavior of the substance during the different stages of drug discovery and development (Boobis et al., 2002).

21.3.7 *In Silico* Prediction of Toxicity Profile

The assessment of drugs toxicity is considered as a critical issue to which developers and researchers have to pay much attention. Conventionally, toxicity was tested by using laboratory animals. In recent improvements, new approaches have been conducted for toxicity optimization, which have been reported to minimize the risks of animal toxicity testing by the replacement with much safer alternatives (Alves et al., 2017). *In silico* toxicology generally refers to predictive science and toxicology computational techniques provide toxicity databases that make it possible to perform QSAR modeling. There are various reasons that stand behind the importance of *in silico* prediction of drugs toxicity,

such as the increasing demand to reduce animal testing, as well as the more suitable toxicity prediction that can be obtained by the use of computational approaches (Toropov et al., 2014). *In silico* prediction methods that are specialized for the prediction of drugs' toxicity can be classified into methods that predict the systemic toxicity and the other methods specifically predict the toxicity for a certain organ. However, other *in silico* models that are concerned with predicting the carcinogenicity as well as the genotoxicity are considered to be more complicated (Roncaglioni et al., 2013).

21.3.8 *In Silico* Prediction of Biological Activity Spectra

The term of biological activity spectrum (BAS) can refer to the compound's intrinsic property that can be represented by various physicochemical and physiological mechanisms of action, pharmacological effects, as well as certain toxicities, such as mutagenicity, teratogenicity, carcinogenicity, and embryotoxicity. Biological activity has been observed to be significantly influenced by the structural properties of the compound. Rapid *in silico* prediction of the molecular properties along with the biological activity have been achieved recently by developing prediction approaches based on the analysis of the QSAR. In order to assess a successful QSAR modeling, it is essential to pay a great attention to the biological measurements, hence accuracy, as well as precision during such analysis, has been widely taken into account (Nantasenamat et al., 2010). Various biological activities were firstly predicted by the PASS computer program which in turn is based on the "biological activity spectrum" concept. However, prediction of biological activities by PASS provides a theoretical estimation regarding the biological potential of the studied compound. It has been reported that about 3750 kinds of activities were accurately predicted by the latest version of PASS program. Furthermore, by the year of 2007, PASS was shown to be capable of predicting more than 3300 kind of biological activities, hence, providing huge data regarding the new biological activities (Lagunin et al., 2010).

21.3.9 *In Silico* Prediction of Active Transport of Drug

The optimization of drugs' transporters has to be included as an important part of any ADME modeling procedure. Transporters are found almost everywhere in the body, in addition to their substrates that were reported to overlap with many drugs, which makes it very essential to predict a drug's transport in the early stages of drug discovery. Various models were developed to predict the effect of transporters on the disposition of drugs which include parameters of drug absorption, distribution, and excretion. The incorporation of transporters prediction programs provides more accuracy while predicting the disposition behavior of drugs (Chang and Swaan, 2006).

21.3.9.1 P-glycoprotein (P-gp)

P-glycoprotein is a transmembrane glycoprotein that is directly encoded by the human ABCB1 gene. It is responsible for the efflux of many harmful compounds inside the cell to the extracellular space, but on the other hand, it also effluxes many drugs out of the cells which can substantially reduce or demolish the activity of many drugs. The crystal structure

of P-glycoprotein revealed that it has a very large ligand binding site which in turn allows many ligands to bind at different positions within the same binding site. P-glycoprotein process of active transport functions differently based on the type of cell. Fig. 21.5 represents different body tissues where active transport by P-gp takes place (Desai et al., 2013). In the past, various homology modeling techniques were used to characterize the structure of P-gp. However, a large number of computational modeling techniques that act by the principle of 2D-QSAR and 3D-QSAR in addition to techniques of molecular docking and pharmacophore modeling have been developed for the prediction of P-gp substrates or inhibitors (Chen et al., 2012). Due to the significant impact of P-gp on ADMET and the effect of its efflux pump on the transport of various drug substances, that in turn has shown a significant change in these substances' pharmacokinetics in addition to the multidrug resistance effect, numerous scientific investigations have been taken into consideration in order to optimize the molecular attributes needed for the understanding of the interactions between P-gp and the substrates of a drug's small molecules (Gombar et al., 2004). In recent studies, docking models were developed on human P-gp to provide a description regarding the structure-based relationship of P-gp binding sites (Moroy et al., 2012).

21.3.9.2 *Breast Cancer Resistance Protein (BCRP)*

Breast cancer resistance protein represents a polytopic transport protein of the plasma membrane that has a molecular weight of 75 kDa that was detected in solid tumors, drug-resistant cells, and hematological malignancies. BCRP has been reported to be highly expressed by body organs that are directly involved in a drug's absorption, distribution, and elimination, such organs include the small intestine, the blood−brain barrier, as well as the liver and kidney, respectively (Rosenberg et al., 2010). Therefore, since BCRP is observably involved in several clinical cases, it has become of a great value to develop new techniques that are cost-effective and helps to evaluate drug transport. Such techniques aim to predict the pharmacokinetic properties of drug candidates in addition to predicting their efficacy, tissue levels, and safety as well. The development of *in silico* techniques is considered as one of the most important prediction techniques regarding BCRP substrates. Recent studies have conducted a new model for predicting the structure and the activity of almost 25 flavonoid analogs. This *in silico* model has confirmed specific requirements for BCRP structure (Chang and Swaan, 2006).

21.3.9.3 *Nucleoside Transporters*

Nucleoside transporters are known to transport the analogs of both synthetic nucleosides and those from natural sources that are mainly acting as anticancer agents (Chang and Swaan, 2006). Nucleoside transporters are considered as a significant issue when developing anticancer and antiviral agents because nucleotide transporters were reported to transport a wide variety of nucleoside-based agents. Basically, there are three main types of intestinal nucleoside transporters, which are CNT1, CNT2, and ENT2 (Billat et al., 2017). *In silico* QSAR models have provided an observation that CNT2 has shown the highest selectivity among the other types, whereas ENT1 have accounted for the broadest inhibition specificity. Recent studies have provided an assessment regarding the transport activity of almost 33 nucleoside analogs (Chang and Swaan, 2006).

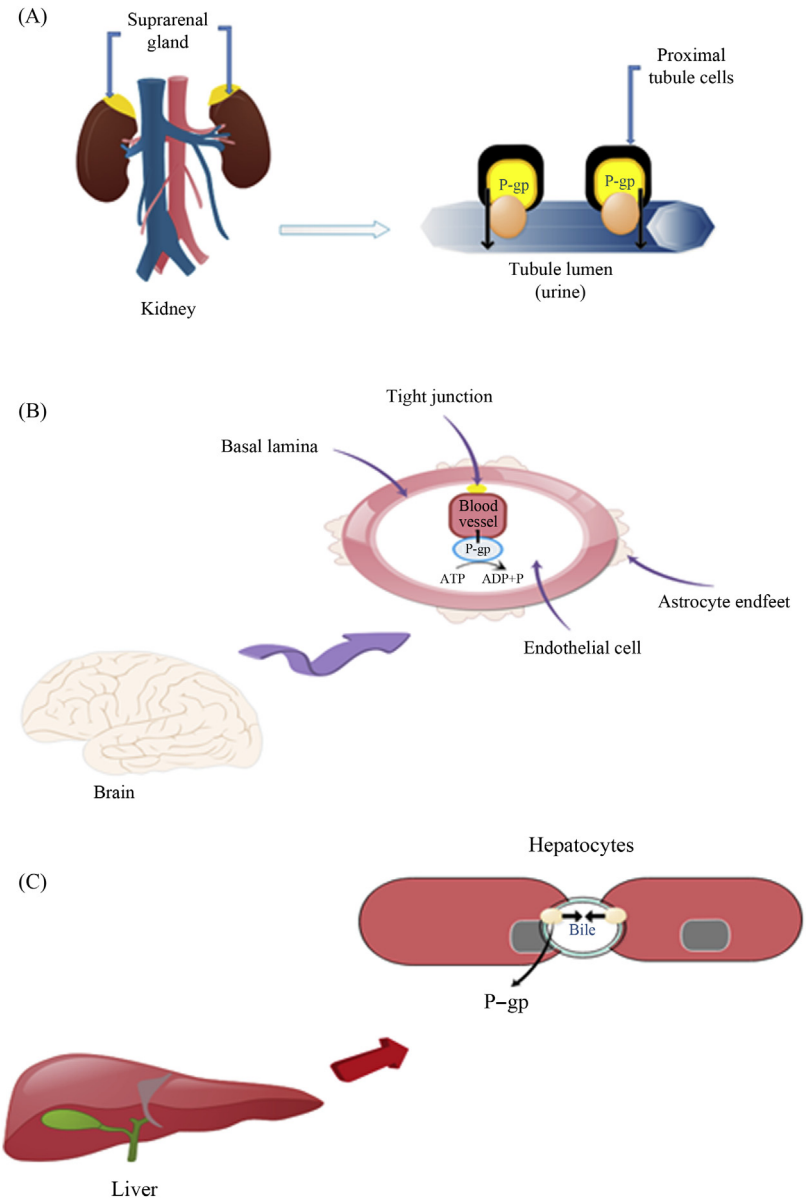

FIGURE 21.5 Three schematic representations that show some of body organs including (A) kidney, (B) brain, and (C) live,r respectively, where P-gp transporter is localized.

21.3.9.4 Human Peptide Transporter (hPEPT1)

The hPEPT1 refers to an oligopeptide transport system that has a considerably low affinity and a high capacity and is basically expressed in the kidney and the intestine and has been reported to affect both the absorption and the excretion of therapeutic agents (Chang and Swaan, 2006). SLC15A1 is the gene that is responsible for encoding the hPEPT1 which in turn determines the influx action of di- and tri-peptides. hPEPT1 has also shown a capability transporting peptide-like drugs such as angiotensin-converting enzyme (ACE) inhibitors and beta-lactam antibiotics in addition to transporting drugs that were shown to be coupled to certain amino acids such as valacyclovir (Billat et al., 2017). A pharmacophore model has been constructed to predict the transport requirements of hPEPT1. The model has been shown to be based on three substrates of high affinity that are the enalapril, Bestatin, and Gly-Sar. This model has demonstrated the application of *in silico* methods while providing high potential for database screening (Chang and Swaan, 2006).

21.3.9.5 Human Apical Sodium-Dependent Bile Acid Transporter (hASBT)

The hASBT is a highly efficient and a highly capable transporter that is shown to be expressed on the intestinal apical membrane. hASBT improves drug absorption by providing additional targets via an assessment of the absorption of bile acids and their analogs (Chang and Swaan, 2006). ASBT system is mainly concerned with small poorly intestinally absorbed molecules or molecules targeting the liver. Delivering these molecules orally via ASBT has been improved currently for small molecules but transporting macromolecules is as yet unexplored (Al-Hilal et al., 2014). Two models have been conducted for ASBT, which are the simplified transport model and the elaborate transport model. These models have provided tracking of the protein's conformational changes in a way that allows it to follow the Na^+ ions movement, and computational models are then combined to the models to provide additional structural information (Alhadeff et al., 2015).

21.3.9.6 Organic Cation Transporters (OCTs)

OCT refers to one of the most abundant transporters of the liver. OCTs are considered as poly-specific membrane transporters that act by mediating the hepatic uptake of hydrophilic compounds that are small and positively charged including dopamine, serotonin, and histamine. In addition to the endogenous transportation function of OCT, it has been also observed to act as a drug transporter that has the capability to transport a wide range of various prescription drugs such as antidiabetic agents and opioid analgesics as well (Chen et al., 2017). There are three main species of OCTs, which are OCT1, OCT2, and OCT3. A pharmacophore model was developed for human OCT1 which provides suggestions regarding the transport requirements of OCT1. Two- and three-dimensional QSAR models have emerged and illustrated the *in silico* modeling discriminating sensitivity of similar transporters (Chang and Swaan, 2006).

21.3.9.7 Organic Anion Transporting Polypeptides (OATPs)

OATP refers to a member of the superfamily of the solute carrier that is localized at the basolateral membrane of hepatocytes. OATP acts by mediating the hepatic uptake of both

endogenous as well as some important clinical compounds. Although OATPs were basically observed in hepatocytes, other observations have reported that they sometimes present in other extrahepatic cancer tissues including those of the colon, breast, pancreas, and prostate (Nagai et al., 2012). OATPs were also shown to influence a drug's plasma concentration via the active transport across various tissue membranes. Presently, more than 11 human OATPs have been identified, and recently, successful meta-pharmacophore models of OATP1B1 have been developed (Chang and Swaan, 2006).

21.3.9.8 BBB-Choline Transporter

Drugs that are intended to act on the central nervous system (CNS) typically face the BBB as the key limiting factor for their permeation. The BBB determines whether the compound is able to pass through the membrane or accumulate, and studies have shown that almost more than 98% of therapeutic compounds accumulate at the BBB due to their hydrophilicity or ionization (Geldenhuys et al., 2010). Since charged molecules are not able to pass the BBB, an alternative method has evolved and is achieved by the native nutrient transporters of the BBB, an example of such transporters includes the BBB choline transporter (BBB-ChT). BBB-ChT has been reported for its ability to deliver choline molecules that are positively charged into the CNS to act as a precursor to the acetylcholine (Ach) transmitter. various therapeutic applications have been observed for the BBB-ChT that include the treatment of hypoxia, ischemia, traumatic brain injury, in addition to neurodegenerative disorders such as Huntington's and Alzheimer's disease (Shityakov and Foerster, 2014).

Various computational methods have emerged for the *in silico* prediction of a drug's uptake into CNS. PLS methods are generally used for the determination of BBB permeation. Both the ligand-based and the comparative modeling methods are considered as the major methods that are used mainly for the development of *in silico* techniques for the modeling of membrane transporters (Allen and Geldenhuys, 2006).

21.4 COMMERCIAL SOURCES FOR ADMET PREDICTION: LIGHT ON RECENT TOOLS

As mentioned previously, the discovery and the development of new drugs are considered as costly and time-consuming processes. Therefore, various computational models have been improved to evaluate experimental findings and to provide the proper suggestions regarding the structures to be synthesized. Nowadays, *in silico* models are being used to make the proper cost-effective decisions regarding drug development in a faster and cheaper way before it is synthesized (Balakumar et al, 2017b; Liao et al., 2011). Recently, an observable application of the computational models has been reported in several disciplines. *In silico* drug discovery methods have been reported to help in identifying the specific drug targets by using certain computational tools (Balakumar et al., 2017b). *In silico* techniques can also provide information regarding the candidate molecules for the development process, and can also check for various properties such as drug-likeness, binding affinity, and binding characteristics (Maithri et al., 2017).

Computer-aided drug design (CADD) is a common computational technology that provides various computational tools regarding the storage, analysis, management, and

modeling of various compounds. Different computer programs are provided by the CADD that have facilitated the process of designing compounds with the desirable physicochemical properties. In the recent few years, CADD have shown a significant role to create computer programs that are able to establish huge pharmacological libraries with the association of new algorithms that aid in the assessment of candidates' potency as well as selectivity (Song et al., 2009). There are other various modern technologies for computational drug development such as combinatorial chemistry, structure-based drug design (SBDD), *in silico* ADMET screening, and virtual screening (Balakumar et al, 2017b). Computer software and the tools involved have also gained wide popularity since information obtained by these tools have provided a significant support to the experimental data and are therefore considered as a complementary aspect to the experimental field (Sharma et al., 2017). A list of the most widely used ADMET prediction software and their applications is provided in Table 21.1 (Liao et al., 2011).

An example of a most commonly used software is QikProp (Schrodinger, Inc.) software. It has the ability to generate and predict 50 molecular descriptors that define the ADMET characteristics of molecules in order to assess the drug-likeness of molecules (QikProp, 2013). The ADMET properties generated by this software for the molecules are compared with known properties of 95% marketed drugs that are orally available, then the properties of the molecules are classified based on a range of values in the software, for example, the oral absorption of drugs has a range of 1%−100 % in the software, molecules with a more than 80% oral absorption are classified as having good oral absorption while molecules with less than 25% oral absorption are classified as having poor oral absorption (Pran Kishore et al., 2012, 2014a, 2014b; Mamta et al., 2014.)

An example of the application of QikProp (Schrodinger, Inc.) software *in silico* prediction of the ADMET properties of the several HIV protease inhibitors drugs is provided in Table 21.2 (Pran Kishore et al., 2014b).

21.5 CHALLENGES AND FUTURE PERSPECTIVES OF *IN SILICO* ADMET PREDICTION

Efforts are increasingly given to develop more applicable and precise ADMET predictive models, though the main obstacle impeding the improvement of new models is basically related to the considerably little data that are available for the creation of durable models that can predict for a wide variety of chemotypes. Therefore, in most cases, it is considered to be unreasonable to expect the new ADMET models to have a performance better than the preexisting models (Clark, 2005). Another obstacle has been reported as a result of the fact that data have to be for the drug being developed and thus it is inapplicable to use data that were previously collected (Burton, 2002). In the future, new better active compounds may be discovered, which in turn may facilitate the development of techniques that search for chemical similarities between various compounds. More sophisticated computational techniques are expected to be developed if more active compounds are discovered, including the techniques of pharmacophore modeling and docking (Sharma et al., 2017; Balakumar et al., 2012; Balakumar et al, 2017b).

TABLE 21.1 A List of the Most Widely Used ADMET Prediction Software and Their Application

Software	Developer	Free for academia?	Applications
ADMET Predictor	Simulation Plus, Inc.	No	ADMET prediction
StarDrop	Optibrium, Ltd	No	ADMET prediction
ADME Suite	Advanced chemistry development, Inc.	No	ADME Prediction
Tox suite	Advanced chemistry development, Inc.	No	Toxicity prediction
ADMEWORKS Predictor	Fujitsu FQS	No	ADMET prediction
QikProp	Schrodinger, Inc.	No	ADMET prediction
MetaDrug	GeneGo, Inc.	No	Metabolism and toxicity prediction
TOPKAT	Accelrys, Inc.	No	Toxicity prediction
PASS	Russian Academy of Medical Sciences	No	Toxicity prediction
METAPC CASETOX	Multicase, Inc	No	Metabolism and toxicity prediction
Meteor Derek Nexus	Lhasa, Ltd	No	Metabolism and toxicity prediction
Bioclipse	Uppsala University, Sweden and EuropeanBioinformatics Institute	Yes	Metabolism prediction
HazardExpert	CompuDrug, Ltd	No	Toxicity
Pro		No	Metabolism
MetabolExpert		No	Toxicity
ToxAlert		No	Metabolism
MEXAlert		No	Metabolism
RetroMex		No	Metabolism prediction

21.6 CONCLUSIONS

In silico computational models are one of the fastest and newest approaches that are involved in the process of drug discovery and development. Due to the accelerated development in the field of pharmaceutics, an increasing demand has arisen regarding the development of more reliable techniques for predicting the pharmacokinetic properties of the new drug candidates as a way to reduce costs and the time that are usually associated with the development of new drugs. The required data vary among the different stages of drug development and preclinical data are considered as an essential requirement when developing new drug candidates. Pharmacokinetic properties including the absorption, distribution, metabolism, excretion, in addition to drug's activity spectra, transport, and toxicity, are considered as the most important properties that need to be predicted in the

TABLE 21.2 Calculation of Various ADMET Properties of FDA Approved HIV Protease Inhibitors by Using QikProp Module of Schrodinger Inc. (Pran Kishore et al., 2014b)

Molecules	MW[a]	SASA[b]	Donor HB[c]	Accpt HB[d]	QPlogP o/w[e]	QPlogS[f]	QPPCaco[g]	QPlogBB[h]	#metab[i]	Human oral absorption (%)[j]	Rule of five[k]
Amprenavir	505.628	717.015	3.5	11.4	2.808	−3.287	262.096	−1.665	4	2	2
Darunavir	547.665	683.329	3.5	13.1	2.434	−2.37	602.619	−1.238	3	2	2
Lopinavir	628.81	862.674	4	9.45	5.1	−5.092	1138.89	−1.209	8	1	2
Atazanavir	718.892	1188.07	3.5	12.7	6.547	−9.052	144.019	−2.87	7	1	2
Indinavir	615.814	1032.85	4	13.9	2.659	−3.787	13.036	−1.291	10	1	2
Nelfinavir	567.785	813.164	4	9.95	4.012	−4.096	306.217	−0.257	5	2	3
Ritonavir	706.917	1155.15	4.25	10.95	6.16	−8.447	82.874	−2.774	9	1	1
Saquinavir	670.85	1047.99	5	13.7	2.503	−4.006	7.492	−2.346	7	2	2
Tipranavir	602.667	924.78	1	10.5	5.56	−7.707	317.973	−1.63	7	1	1

[a]*Molecular weight.*
[b]*Total solvent accessible surface area (SASA) in square angstroms using a probe with a 1.4 Å radius, range 95% of drugs (300.0−1000.0).*
[c]*Estimated number of hydrogen bonds that would be donated by the solute to water molecules in an aqueous solution, range 95% of drugs (0.0−6.0).*
[d]*Estimated number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution, range 95% of drugs (2.0−20.0).*
[e]*Predicted log of the octanol/water partition coefficient, range 95% of drugs (−2−6.5).*
[f]*Predicted log of aqueous solubility* S *(mol/L), range 95% of drugs (−6.5−0.5).*
[g]*Caco2 cell permeability in nm/s, range 95% of drugs (<25 poor, >500 great). Caco-2 cells are a model for the gut-blood barrier. QikProp predictions are for non-active transport.*
[h]*Predicted brain/blood partition coefficient, range 95% of oral drugs (−3.0−1.2).*
[i]*Number of likely metabolic reactions; range 95% of drugs (1−8).*
[j]*Predicted human oral absorption on 0 to 100% scale (>80% is high and <25% is poor).*
[k]*umber of violations of Lipinski's rule of five. The rules are: mol_MW < 500, QPlogP o/w < 5, donor HB ≤ 5, accpt HB ≤ 10. Compounds that satisfy these rules are considered druglike (the "five" refers to the limits, which are multiples of 5).*

early stages of drug development. There are various physicochemical properties that can be predicted by the new models of *in silico* approaches, such as the lipophilicity, solubility, hydrogen bonding, as well as the permeability across the biological membranes.

Various transporters have shown to contribute to some drugs' activities, and hence, affect their ADMET properties. Such transporters are summarized as P-glycoprotein, breast cancer resistance protein, blood−brain barrier choline transporter, hPEPT1, OATP, and OCTs. Nowadays, a wide variety of new commercial software tools for prediction purposes are available including the CADD, combinatorial chemistry, SBDD, virtual screening, and *in silico* ADMET screening. The few databases available for newly developed drugs and the inability to apply precollected data are still considered as challenges for researchers and developers. In the future, more applicable and precise approaches are expected to be developed providing higher accuracy and faster procedures.

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ABBREVIATIONS

2D-QSAR	two-dimensional quantitative structure−activity relationship
3D-QSAR	three-dimensional quantitative structure−activity relationship
Ach	acetylcholine
ADMET	absorption, distribution, metabolism, excretion, and toxicity
BAS	biological activity spectrum
BBB	blood−brain barrier
BBB-ChT	Blood−brain barrier choline transporter
BCF	bioconcentration factor
BCRP	breast cancer resistance protein
BP	boiling point
CADD	computer-aided drug design
CNS	central nervous system
hASBT	human apical sodium-dependent bile acid transporter
HB	hydrogen bonding
hPEPT1	human peptide transporter
kDa	kilodalton
LogP	partition coefficient
MP	melting point
OATPs	organic anion transporting polypeptide
OCTs	organic cation transporters
P-gp	P-glycoprotein
PLS	partial least squares
PPB	plasma protein binding
PSA	polar surface area
QSAR	quantitative structure−activity relationship
QSPR	quantitative structure−property relationship
SBDD	structure-based drug design
VD	volume of distribution

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