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Review Article

Theme: Advancements in Modified-release Oral Drug Delivery - Delivery throughout the Gastro-intestinal Tract

Simulation Models for Prediction of Bioavailability of Medicinal Drugs—the Interface Between Experiment and Computation

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Abstract. The oral drug bioavailability (BA) problems have remained inevitable over the years, impairing drug efficacy and indirectly leading to eventual human morbidity and mortality. However, some conventional lab-based methods improve drug absorption leading to enhanced BA, and the recent experimental techniques are up-and-coming. Nevertheless, some have inherent drawbacks in improving the efficacy of poorly insoluble and low impermeable drugs. Drug BA and strategies to overcome these challenges were briefly highlighted. This review has significantly unravelled the different computational models for studying and predicting drug bioavailability. Several computational approaches provide mechanistic insights into the oral drug delivery system simulation of descriptors like solubility, permeability, transport protein-ligand interactions, and molecular structures. The *in silico* techniques have long been known still are just being applied to unravel drug bioavailability issues. Many publications have reported novel applications of the computational models towards achieving improved drug BA, including predicting gastrointestinal tract (GIT) drug absorption properties and passive intestinal membrane permeability, thus maximizing time and resources. Also, the classical molecular simulation models for free solvation energies of soluble-related processes such as solubilization, dissolutions, supersaturation, and precipitation have been used in virtual screening studies. A few of the tools are GastroPlus™ that supports biowaiver for drugs, mainly BCS class III and predicts drug compounds' absorption and pharmacokinetic process; SimCyp® simulator for mechanistic modelling and simulation of drug formulation processes; pharmacodynamics analysis on non-linear mixed-effects modelling; and mathematical models, predicting absorption potential/maximum absorption dose. This review provides *in silico*-experiment annexation in the drug bioavailability enhancement, possible insights that lead to critical opinion on the applications and reliability of the various *in silico* models as a growing tool for drug development and discovery, thus accelerating drug development processes.

KEY WORDS: bioavailability; computational models; solubility; medicinal drugs; dissolution.

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Abbreviations: *ADME*, absorption, distribution, metabolism and excretion; *Ag*, silver; *AP*, absorption potential; *MAD*, maximum absorption dose; *NMs*, nanomaterials; *PBPK*, physiologically-based pharmacokinetic; *PCs*, partition coefficients; *QSAR*, quantitative structure-activity relationship; *ORMUCS*, Ordered multi-categorical classification method using the simplex technique method.

INTRODUCTION

Overview of Bioavailability (BA) of Medicinal Drugs—The "bottleneck"

The drug approval journey encounters several challenges, such as high costs, safety (1), tight timelines, most importantly, the need for the drug to demonstrate efficacy and safety (2). Bioavailability could be another stumbling block to discovering and developing efficacious drugs if not addressed in this journey. First, an active pharmaceutical ingredient (API) must dissolve in the gastrointestinal tract before being absorbed through the gut wall (3). When a tablet is swallowed, it disintegrates to release the active pharmaceutical ingredient (API). After that, it enters the

bloodstream and passes through the liver. Finally, it travels to the site of action to produce the desired therapeutic effect in the systemic circulation. Still, some APIs would be lost to metabolism due to the first-pass effect or other factors during this long trip (delivery) (4,5).

In simple terms, bioavailability is the proportion of administered dosage of the drug that reaches the systemic circulation and is available to produce its desired effect. The bioavailability studies are usually performed by measuring the concentration of the drug in the blood after administration of the drug following systemic study protocol and documented over time. The systemic protocol is crucial for clinical trials in early drug development.

Intravenous administration results in almost 100% bioavailability among all drug dosage forms. Nevertheless, oral drug formulations are preferred due to their better physical and chemical stability and higher patient compliance—85% of the most sold drugs in the USA and Europe are orally administered (3). However, achieving high bioavailability for orally administered medications is considered a "bottleneck" in drug discovery. Moreover, almost half of potential chemical entities and drugs currently in the developmental stage are categorized as "practically insoluble" (3,6). Figure 1 highlights the different drugs classes according to the Biopharmaceutics Classification System (BCS), a system to differentiate the drugs' solubility and permeability (7).

It is often misperceived that high doses of active ingredients can be given to patients to achieve therapeutic efficacy. Nonetheless, there may be a risk of toxicity, limiting the drug's tolerability. Optimizing a drug's bioavailability will, in turn, reduce its therapeutic dose, hence, reducing associated side effects.

Drug bioavailability and strategies to overcome these challenges were briefly highlighted in the following sections. However, this review emphasized the different computational models for studying and predicting drug bioavailability. It further provides a platform to understand the "interface" between the experiment and *in silico* bioavailability studies. Hopefully, it would lead to some critical opinion on the applications and reliability of the various *in silico* models as a growing tool for drug development and discovery.

CHALLENGES OF DRUG BIOAVAILABILITY IN DRUG DISCOVERY

Many barriers could preclude high drug bioavailability (8,9). Although there is no systematic classification for the contributing factors that influence drug bioavailability, we opted to classify these barriers into four categories. They include (1) drug product–related factors, such as the physicochemical properties (10) of the drug itself and the formulation/composition of the drug dosage form/product; (2) features of the human body, including genetics, age, specific disorders, gastric emptying rate (11), and an individual's level of physical activity (12); (3) route of administration (13); and (4) drug-ligand interactions (12,14), including drug-drug (15), drug-food (16), or drug-enzyme (induction/inhibition) (17,18) interactions.

An initial pharmacokinetics (PK) assessment is critical in resolving the limiting barriers of bioavailability, although it is utterly impossible to address/assess all the above factors in a single systematic protocol to attain "maximum bioavailability". Hence, it is the appropriate strategy through which the bioavailability can be optimized.

ASSESSMENT OF DRUG BIOAVAILABILITY

Experimental bioavailability tests are performed for a new drug to determine important PK parameters such as absorption rate, the extent of absorption, excretion rates, and metabolism and elimination. These essential pharmacokinetic parameters are critical for establishing dosage regimens. In early drug discovery phases, profiling a drug compound involves individual assessments of solubility, permeability, and susceptibility to the first-pass metabolism—these are the three most likely contributors to inadequate oral bioavailability. An initial evaluation of absorption potential can be performed via computational screening, and high throughput *in vitro* assays are typically carried out to prioritize compounds for *in vivo* studies.

The Biopharmaceutics classification system (BCS) has been one of the most potent predictive tools created to promote product development in recent years. Herein, we refer to several literature reviews that have thoroughly covered this topic (19–27): the current review's focus. Nevertheless, we highlight the crucial concept for experimental bioavailability assessment to understand the basis of the *in silico* counterparts utilized to study and predict BA.

STRATEGIES TO OVERCOME DRUG BIOAVAILABILITY ISSUES

Reports have shown that approximately 90% of the drug candidates derived through high throughput screening exhibit low aqueous solubility (28,29). The poor aqueous solubility of these drugs leads to an erratic bioavailability with subsequent unwanted side effects. Undoubtedly, oral bioavailability is the most imperative attribute of the drug molecule to be considered in its selection during the drug discovery stage.

Among the drug routes of administration, oral delivery is usually synonymous with low drug bioavailability at the action site (1), despite its superior strengths compared to various other delivery routes. Its advantages are pretty overwhelming, including ease of administration, sustainable delivery, desirable therapeutic effects, probable long shelf life solid formulation, intensified immune response, and patient compliance (24). Improving oral drug bioavailability is the most realistic approach (8). Thus, it is recognized and regarded as the most attractive drug pathway (8). The drugs orally administered pass through and absorb in a small GI tract compared to other segments, including small (jejunum and ileum) and large intestines (cecum, colon, rectum). The drugs face barriers categorized as biologic and technical; thus, they denature the orally administered drug, prevent successful absorption in the target, and create properties addressing the barriers/scaling up complications. Such surrounding factors as a drug's residence time, pH, and diversity of bacteria in different segments influence drug absorption. The causes of drug bioavailability issues in the oral route

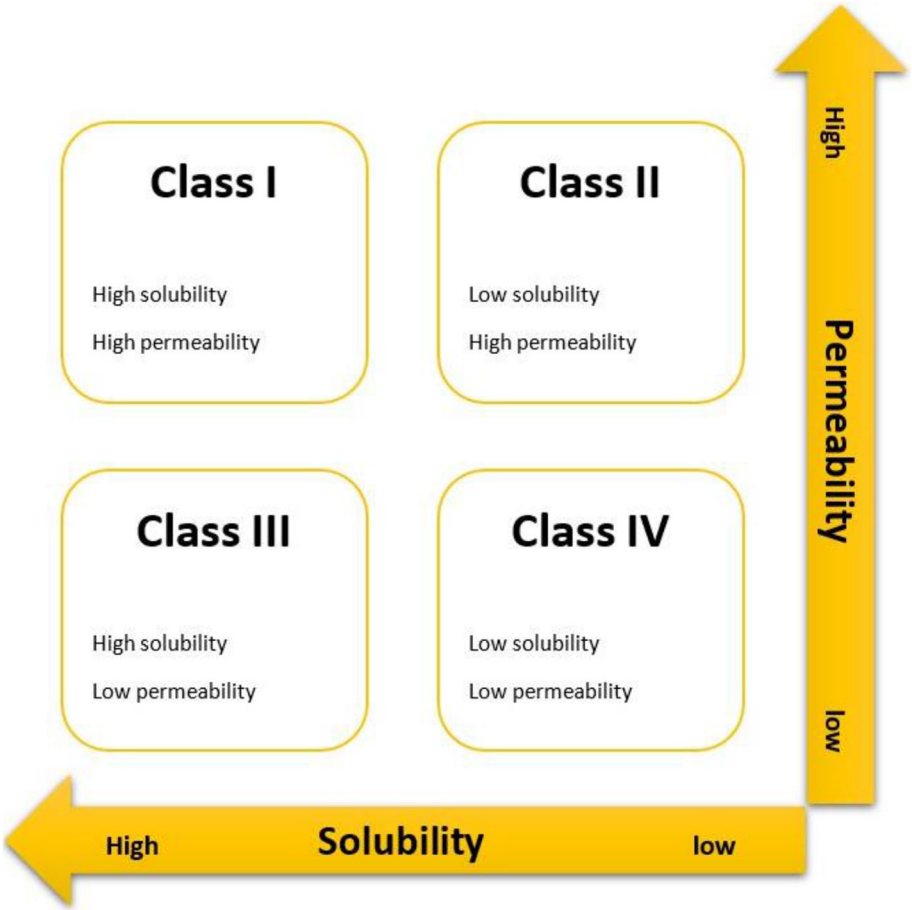

Fig. 1. Biopharmaceutical Classifications Systems of drugs based on solubility and permeability properties; class I, class II, class III, and class IV

include low drug solubility in water, poor dissolution rate, poor permeation of drug molecules across the membrane, and pre-systemic metabolism (first-pass metabolism). Additionally, degradations of the drug or chemical interactions with the gastrointestinal tract, drug efflux pumps, crystal packing, polymorphism, molecular weight, and inter- and intramolecular hydrogen bonding lead to low drug bioavailability (30,31). These shortcomings of oral administration pose critical concerns because the drugs' pharmacokinetics data obtained from the oral pathway has remained challenging.

Supposedly, drug delivery via alternative routes should have been absolute for drug administration because high drug bioavailability is attainable. However, they also have weaknesses and encounter various specific barriers against drug delivery (31). Thus, the oral drug routes have remained the most favourable for obtaining targeted therapy (24). Moreover, poorly water-soluble drugs have been shown to cause clinically severe problems (32) such as high patient costs, inter-patient variability, and increased risks of toxicity/death.

The scientists from the academia and R & D sectors have shown a noticeable interest in developing new strategies for addressing the poor solubility/bioavailability issues associated with many drug candidates. Poor aqueous solubility and low permeability are the two leading factors causing the poor bioavailability of many drug candidates. The enhancement of insoluble BCS-II and BCS-IV drug candidates provides the drug molecules possible treatment of a range of challenging diseases such as type II diabetes (33), cancer (34), and inflammatory infections. For instance, self nano-emulsifying drug delivery systems (SNEDDs) were used to improve the drugs' solubility and provide a large interfacial area to increase the absorption rate of insoluble drugs (33,35). However, these drugs have poor bioavailability and solubility issues, becoming the primary hurdle for commercializing the new pharmaceutical products. The strategies for improving the bioavailability of the potential drugs have been classified into the main classes discussed below.

Physical Methods

More than 85% of pharmaceutical dosage forms have APIs in the crystalline state (31). Owing to stability issues of the amorphous particles, the crystalline form of the APIs is preferably chosen for dosage form development. Small particles have a large surface area, leading to a high dissolution rate and subsequent rapid BA compared to the macroparticles. Particle size reduction techniques, including micronization and milling, are the two established techniques for reducing the size of the drug compounds. Micronization through jet milling can effectively reduce particle size <5 μm (36,37).

Furthermore, ball milling approaches are employed to produce nanocrystals with particle sizes < 300.0nm (34). The recent literature suggests that the cocrystal method has

become the most popular approach for improving the solubility and bioavailability of poorly water-soluble drugs. A cocrystal is a crystalline structure formed by two or more molecular entities, where the entities are linked through weak intermolecular forces, including hydrogen bonding (38). The majority of cocrystals, where a single API (active pharmaceutical ingredient) is co-crystallized with non-active co-formers, have been investigated. Cocrystals lead to more stable crystal forms with better solubility profiles and enhanced bioavailability. For example, the cocrystals of carbamazepine-saccharine and acetazolamide-nicotinamide have exhibited enhanced bioavailability compared to their raw counterparts (39,40). Furthermore, several multidrug cocrystals have also been recently reported, where the drug molecules are exploited as conformers to yield highly water-soluble drug-drug cocrystal (41). In contrast to the physical mixture of the two or three APIs, the multidrug cocrystals demonstrated boosted bioavailability (42).

Chemical Methods and Medicinal Chemistry Tools

Medicinal chemists prioritize the bioactivity and bioavailability attributes of the new potential molecules during the early discovery stages of new APIs. Therefore, drug design strategies primarily focus on the significant oral absorption of the new molecules during the early stages of the lead selection and optimization process. For the ideal drug design strategies, understanding the physicochemical properties and PK of the drug molecules are the utmost parameters to consider. Moreover, pharmacodynamics (PD), which describes the behaviour of drugs on the body, requires consideration. This background provides an intelligent way to design the new potential drug molecule.

The therapeutic potential of drug molecules builds on their physicochemical properties. For ionizable drug compounds, a change in pH of the medium is a very effective tool for increasing drug solubility. Solubility of most drugs, either weak acids (low pKa) or weak base (high pKa), is easily increased by a change in the pH and enhanced bioavailability. In addition, salt formation has also been reported as one of the easy and well-established techniques for increasing solubility and dissolution of the acidic and basic drug compounds (43). The interaction/permeability of the salt form of the drug molecules is more consistent and faster than the pure drug. Among the physical methods for improving the bioavailability of the drugs, the concept of prodrug has become an expendable approach (44). Prodrugs are the inactive derivates of drugs formed inside the body through hydrolysis or enzymatic reactions. Prodrugs occur through covalent interaction by the conjugation of the chemical moiety. However, the newly attached groups should be easily cleavable and reversible to release the actual drug when entering the bloodstream. Therefore, the drug molecules with polar functional groups, including hydroxyl, amino, carboxyl, and phosphate groups, are the most suitable choices for converting to high lipophilic ester or alky derivatives through prodrug strategies.

Prodrugs, in which the newly attached group does not mask the chargeable groups but plays the transporter role, have become attractive classes for drug delivery scientists. The peptides, like Oligopeptides, are the most effective transporters to carry a variety of drug molecules into the bloodstream successfully. For example, the bioavailability of acyclovir and ganciclovir has been improved through the peptide transporters' prodrug technique (44). Valquinidine, a quinidine prodrug synthesized through the peptide moiety, has recently shown enhanced bioavailability (45). Hence, a prodrug concept is an instrumental approach exploited for the targeted drug delivery application with maximum therapeutic output.

Formulation Strategies

Formulation strategies for addressing the poor bioavailability issues of several available marketed drugs and the drug candidates in the development pipeline have become the most economical suitable choice for drug delivery scientists. In contrast to chemical modifications/discovery of the new drug molecules using sophisticated medicinal chemistry tools, formulation development through available safe excipients is a very accessible and time-saving approach. Numerous formulations have been reported for addressing the erratic bioavailability of many drug compounds (27,30,37,46–48). These approaches include nanosuspensions, micronization, nanoemulsions, nanocrystals, polymeric nanoparticles, solid dispersion, and complexation. Other techniques are liposomes, co-solvents, micelles, phytosomes or nano-phytosomes, solid lipid nanoparticles (SLNs), lipid polymer hybrid nanoparticles (LPHNs), polymer hybrid microspheres, self-emulsifying drug delivery systems (SEDDs) (Fig. 2). The application of nanoparticles has become the most successful formulation approach to improve the poor drug bioavailability. This technique allows high drug adhesiveness to the epithelial membrane, high concentration gradients, high saturation solubility, and improved dissolution. The bioavailability of poorly soluble drugs was enhanced by 80 folds using nano-suspensions and nanocrystals techniques. Such drugs include dexibuprofen, silymarin, domperidone, anticancer, glibenclamide, artemether, lumefantrine, glimepiride, and many antibiotics (25,49–51).

Co-solvency or Combination of Solvents

Co-solvency is a classical technique that enhances the aqueous solubility of poorly water-soluble drugs utilizing water-miscible or partially miscible organic solvents by reducing the interfacial force between the aqueous solution and hydrophobic solute (52). It is simple and effective (53). Such co-solvents are sorbitol, ethanols, and polyoxyethylene glycol. Co-solvency is one of the most widely used approaches, and its formulation advantage for the poorly soluble drug can be achieved for both oral and parenteral. The solubility of antidiabetic medications (e.g. repaglinide) (53) has been enhanced with this approach. Also, the poor solubility of ethylparaben and enrofloxacin drugs has been improved. The use of surfactants enhances the solubility and dissolution of poorly soluble drugs and stabilizes drug suspension because of their amphiphilic nature (23). This is referred to as the micellization technique. The mixed micelles are designed based on the drug physical and chemical properties and the compatibility between the micelle and drug substance. Surfactants decrease surface tension to

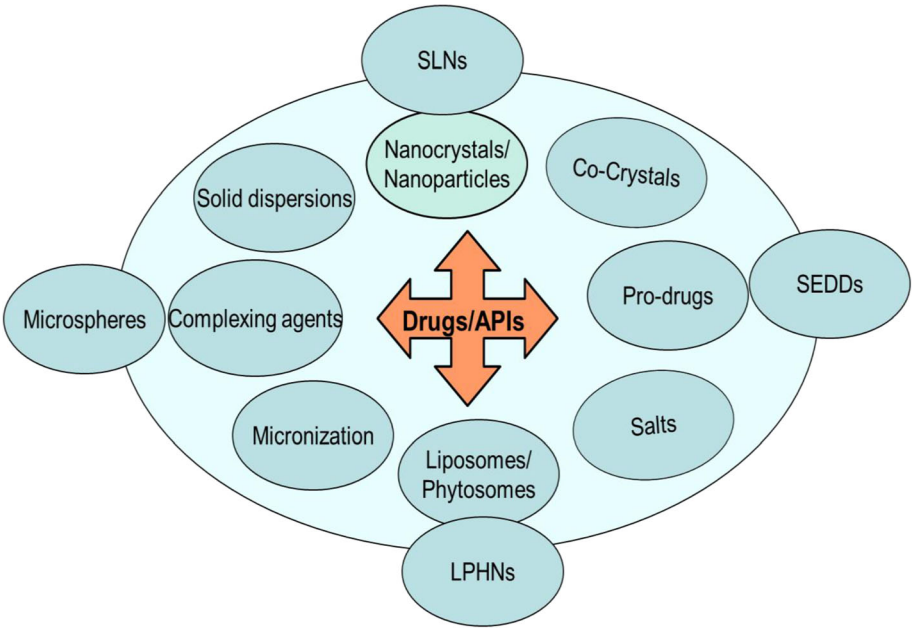

Fig. 2. Different strategies for enhancement of solubility/bioavailability.

enhance the dissolution rate of lipophilic drugs in the aqueous medium. The engineered micelle structure provides a high solubilization capacity of the bioactive compounds (54). Besides, fabricated micelle has a characteristic control release due to the mixed micellar formulation. Micelle is formed when the surfactant's concentration exceeds the critical micelle concentration (CMC), ranging between 0.05 and 0.10 % (55). Some examples of poorly soluble drugs enhanced using micellar solubilization include repaglinide, glimepiride, antidiabetic agents. Non-anionic surfactants such as glycerides, low molecular weight mono- and di-fatty acid esters (polyethylene glycols), and polyoxyethylated castor oil are commonly used surfactants (35,37).

Complexation Strategy

Complexation is crucial for enhancing poorly soluble drugs' solubility and dissolution rate (55). It is among the most successful approaches used to enhance drug bioavailability. For example, cyclodextrins (CDs) are complexing agents often used (56). They are cyclic torus-shaped molecules with a hydrophilic outer surface and a hydrophilic central cavity that accommodate various lipid-loving drugs, which allow effective improvement when included in the drug's drug formulation physicochemical properties. Such characteristics are bioavailability, stability solubility, and dissolution rate. β-cyclodextrin type is more suitable for the practical purpose among cyclodextrins (56). CDs are obtained from starch involving biocatalytic conversion and form inclusion complexes with the drug, thus taking up a whole molecule or part of it into the cavity. In recent years, they have found increasing applications in pharmaceutical formulations. The prepared inclusion complexes with cyclodextrin have successfully overcome the solubility of poorly water-soluble drugs. The formulations containing lipids have improved the orally administered drugs by increasing the bioavailability of poorly water-soluble drugs and changing their release profile. Moreover, such lipids are readily available with specific properties. Examples of complex drugs with β-CD are Prostarmon-E™ sublingual tablets and piroxicam.

However, lipid formulations including SLNs, phytosomes, nano-phytosomes, lipid dendrimer hybrid nanoparticles, LPHNs, and SEEDs have become the most attractive formulation approach. They have substantially enhanced the bioavailability of several challenging drug molecules (51,57,58). Among the lipid formulations, LPHNs and SEEDs have tremendous attraction due to their exceptional drug loading potential and stability compared to the conventional lipid formulations. In a lipconsensus model polymer hybrid system, both the hydrophilic and hydrophobic entities are embodied. A lipid-polymer hybrid system consists of the lipids layer that are made up of hydrophilic and hydrophobic moieties (phospholipids) used to deliver hydrophophilic and hydrophobic drugs, even protein (59)..Therefore, this system opens up a window for delivering different classes of drug compounds. SEEDs have the potential to effectively release the drugs that belong to BCS-II, BCS-III, and BCS-IV with 100% entrapment efficiency to the bloodstream. This system completely protects the drug from degradation in the GI tract and delivers the drug to the lymphatic system (60,61).

ENHANCEMENT OF DRUG BIOAVAILABILITY USING COMPUTATIONAL MODELS

Several computational modelling approaches have been put forward to provide mechanistic insights into the oral drug delivery system simulation (62–64). Computational techniques are now available to help predict and provide insights into the properties involved in gastrointestinal tract drug absorption. While some mechanical models fall into dispersion models, the remainder falls into compartmental models. Typically, the dispersion models define the GIT as a single

tube with varying parameters. However, PK-Sim employs a dispersion model that allows quantitative pharmacokinetics (PK) predictions in human and pre-clinical animal models. The GIT is modelled as a cylindrical medium with varying properties (65–67). In addition, this software considers the characteristics of the species, gender, age, and patient population, providing the intestinal absorption and the drug distribution in the organs.

Furthermore, drug transit in the GIT is modelled by introducing a transit function in such a model. The transit function computes part of the drug present in a segment of the GIT, implying that the swallowed drug is instantaneously transmitted to all the areas of the GIT, which might be small in quantity. In light of this, such models cannot capture accurately the physiologically realistic gastric and intestinal emptying times (68).

On the other hand, the compartmental models represent the GIT as a series of compartments, and each has a uniform concentration. The absorption compartment and transit (CAT) model is a well-known compartmental GIT model developed by Yu *et al.* (69,70). This model divides the GIT into one stomach segment, seven small intestine segments, and one colon segment, totalling nine. Also, similarly to the dispersion models, the CAT model suffers from the instantaneous drug presence within all the compartments. The CAT model serves as a precursor to other models such as the Advanced Compartmental Absorption and Transit (ACAT) model (71) and the Dissolution Absorption and Metabolism (ADAM) model (72). While the new models include the first-pass metabolism, colon absorption, and gut wall metabolism, they still exhibit similar problems encountered by the CAT model. Many software packages have emerged with integrated oral absorption models with physiologically dependent pharmacokinetics (PBPK) structure and compound databases to provide predictive tools for drug design and pharmacokinetics studies (70,73).

Statistical models dependent on regression analysis from several descriptors and the response of interest, such as solubility, permeability, and interactions with transport proteins, have become extremely common, owing partly to their ease of use and the speed with transport which predictions can be made. These multivariate data analysis models are based on quantitative structure-activity relationships (QSAR) used in medicinal chemistry to investigate the potency of a set of ligands to estimate the effectiveness of new analogues. QSAR phenomenon emerged in the early 1970s and was based mainly on the correlation between a single univariate property and the response in an activity screen. More predictive, complex models for activity were developed later based on several molecular properties (multivariate). Different linear and non-linear methods such as partial least squares projection to latent structures (PLS), support vector regression/ machines (SVR/SVM), random forest (RF), and artificial neural network (ANN) are the most widely used methods for predicting absorption related properties such as solubility, permeability, transporter interactions (74,75). These models are often combined with so-called consensus models to produce more precise predictions (76). All the models have one thing in common: they extract descriptors linked to the response parameter. Several different steps are taken to certify that the extracted descriptors are correlated to the response (and not just a function of, e.g. a biased dataset). Usually, resampling measures examine model robustness and relevance of descriptors. Cross-validated R2 (Q2), bootstrapping, and permutation tests are examples of such. Q2 is a statistical measure that estimates the model performance when subsections of the training set in the model generation are excluded (76).

Solubility Prediction

The thermodynamic solubility of a drug or compound fully non-ionized at a pH is known as intrinsic solubility. The parameter is determined after the solid (stable polymorph) equilibrium and the dissolved form has been established. Computational models that predict this property from molecular structure alone usually depends on multivariate data analysis (e.g. methods such as PLS, ANN, SVR, and RF). These methods make available quantitative results. The prediction accuracy ranges from 0.5 to 1 log10, which means that a predicted solubility value varies by up to 3–10 times from the experimentally determined value (77,78). Lipophilicity, non-polar surface area, molecular flexibility, and aromaticity/π–π interactions tend to be essential molecular descriptors for intrinsic solubility (77,79,80). The intrinsic solubility value is not a physiologically important measure for several ionizable compounds. Instead, it should be viewed as a physicochemical fingerprint of the molecule.

A drug is exposed to a wide variety of pH after oral administration. The pH of the stomach is acidic (1.7–3.3; median of 2.5) when in the fasted state, while the pH of the distal jejunum is neutral or slightly basic (6.5–7.8; median of 6.9) (81). The pH, therefore, remains at a high level for the fasted distal part of the ileum and colon, with an average pH of 8.1 and 7.8 reported, respectively (82,83). In addition to the pH gradient, bile secretion in the duodenum forms lipoidal nano-aggregates, such as mixed micelles and vesicles, in the intestinal fluid consisting of phospholipids and bile salts. Thus, the final solubility of drugs in the intestinal fluid is greatly influenced by changes in pH and the existence of nano-aggregates with high solubilizing potential.

As a result, solubility varies by person and is determined by food composition and prandial state (physiological condition when a meal is taken) (84). Hence, solubility prediction is complex in intestinal fluids. The most convenient approach is to estimate intrinsic solubility and pKa using the *in silico* models, then insert these values into the Henderson–Hasselbalch equation. *In silico* models for predicting solubility in fasted human intestinal fluid (HIF) or bio-relevant dissolution medium mimicking this fluid have recently appeared (85).

The modelling of solubility using the thermodynamics cycle (Fig. 3) is one of the recent principles investigating the fundamental underlying mechanistic solubility and the insights into the property (86). An attempt at the thermodynamic cycle model describes the solubility better than the QSRP models (86). The intrinsic solubility and the Gibbs free energy change are given as:

$$\Delta G_{(sol)} = \Delta G_{(sub)} + \Delta G_{(hydr)} - RT \ln S_o V_m$$

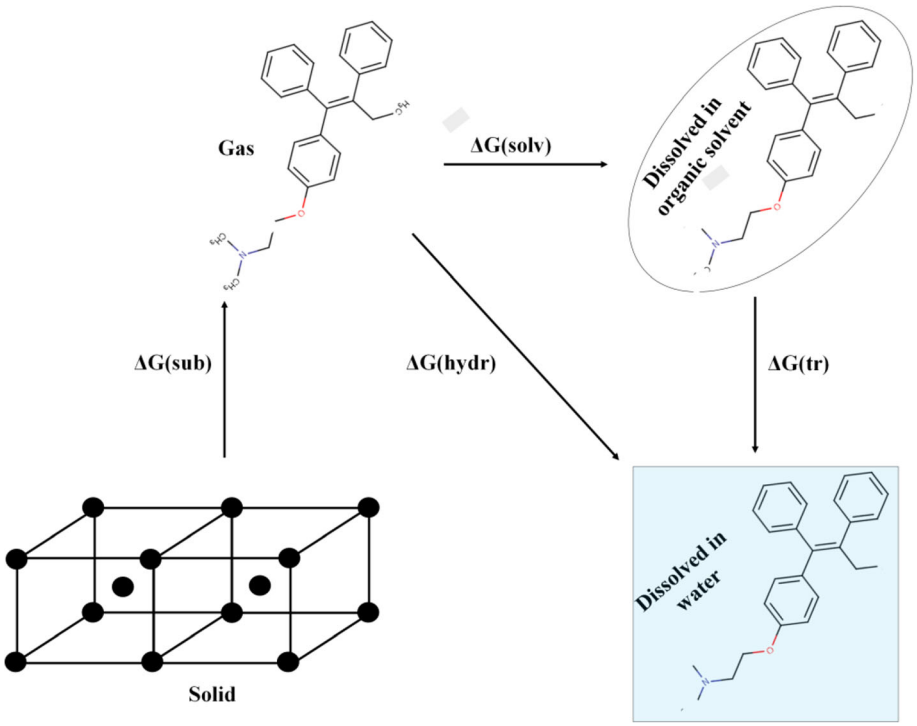

Fig. 3. The thermodynamic solubility cycle model. Δ*G*sub—Gibbs free energy of sublimation, Δ*G*solv—Gibbs free energy of solvation, Δ*G*hyd—Gibbs free energy of solvation, and Δ*G*tr—Gibbs free energy of transfer (86).

$\Delta G_{(sol)}$, $\Delta G_{(sub)}$, and $\Delta G_{(hydr)}$ are, respectively, the Gibbs free energies of the solution, sublimation, and hydration. R is the molar constant of the gas and T, the temperature (K). The S_o and V_m terms are the crystal's intrinsic solubility and molar volume, respectively.

The Gibbs free energies of all the three steps of the thermodynamic cycle can be calculated theoretically (87). $\Delta G_{(sub)}$ can be calculated by modelling the potential-based lattice energy and dynamics simulations, while Gibbs free energies of hydration and solvent can be estimated using quantum mechanics. The last term, $\Delta G_{(tr)}$, can be solved from the calculated log *P*. Moreover, some stepwise computational modelling methods have also been used to evaluate the terms in this cycle to model the free energies of hydration and solvation in pure melts and amorphous matter (87,88).

Simulation Model of Drug Permeability Through Biomembrane

Although oral absorption can be affected by many factors, including physicochemical, physiological, or formulation-related, two essential properties that have been fundamentally acknowledged to play the most critical roles in human intestinal absorption of drugs include permeability and solubility (89). For decades, various *in vivo* and *in vitro* experimental models have been used to predict drug candidates' permeability. Most recently, however, computational models have also been employed to predict passive intestinal membrane permeability with the advantage of maximizing time and resources, thereby conveniently reducing the time it takes for hit compounds to follow the developmental process into stage 4. While the permeability of compounds is related positively to lipophilicity, hydrogen bond capacity and molecular size are negatively associated with it (90,91). As a result of passive diffusion across the lipoidal membrane, membrane permeability is typically high, and absorption is not permeability-limited for compounds in the lipophilic, B-r-o-5 chemical space. Highly polar and larger molecules, on the other hand, often exhibit permeability-limited absorption (92). However, intrinsic membrane permeability is usually high for lipophilic drugs. Various cellular mechanisms can play a role in the transport rate, and the ease at which highly lipophilic compounds cross cells. Entrapment in the membrane, non-specific binding to intracellular proteins, and specific binding to membrane-bound efflux transport proteins can all be important determinants of cellular transport rate and extent (93,94).

Similar computational model techniques and multivariate tools (i.e. PLS, ANN, SVR, RF) are used to predict drugs' permeability (74). For the validation test sets, the accuracy of *in silico* models is 0.39–1.43 log10 units (95). *In silico* models for predicting the effective permeability P_{eff} have also been developed, with accuracy comparable to cell-based models (76). However, since the available dataset is limited, the P_{eff} models are typically analyzed with fewer test compounds (generally nb10). Thus, computational models for membrane permeability prediction can be broadly divided into two, viz, qualitative and quantitative models.

Qualitative Models

In a bid to develop qualitative models to predict membrane permeability, researchers first examined an array

of compounds classified to have attained the phase II stage of the drug development process (96). It is believed that compounds crossed this stage are adequately absorbed and possess other essential properties that make them suitable to be absorbed orally. While using a computer-based multifactorial approach, these compounds were classified as either drug-like or non-drug-like. Qualitative models of drug-likeness have been developed by scrutinizing drug-like compounds using systematic patterns in their structures, comparing them with non-drug-like compounds and analyzing utilizing a set of molecular descriptors (97–99). Qualitative models have been widely employed due to the lack of definitive experiments to predict membrane permeability and the lack of allowance for studying many compounds. However, this model has the drawback of being too easy in that it is devoid of the complexity to differentiate between drugs and non-drugs succinctly. The following rules provide molecular descriptors [6–11] used in qualitative models to predict oral bioavailability and permeability of compounds.

A. **Rule-of-Five:** This rule was introduced by Lipinski and co-workers and has been extensively used as a qualitative predictor of absorption and permeability of oral compounds. Lipinski reported four important molecular descriptors capable of predicting a compound's drug-likeness in a study involving 2245 phase II compounds analyzed. These include the number of hydrogen bond donors (greater than five), hydrogen bond acceptors (greater than ten), calculated octanol/water partition coefficient (more than five), and molecular weight (more than 500). The study concluded that if greater than two limits are exceeded, the compound is not likely to be a drug (100). Recently, the clinical relevance of this rule has been subjected to scrutiny.
B. **Verber's Rule:** Verber and co-workers proposed this rule after analyzing the oral bioavailability of about 1100 compounds in rats (101). According to them, molecular predictors of good oral bioavailability believed to be independent of molecular weight, unlike rule-of five include molecular flexibility (measured by the number of rotatable bonds; 10 or fewer rotatable bonds) and polar surface area (PSA equal to or less than 140 $Å^2$) in rats. However, studies show Verber's rule cannot predict oral bioavailability with high confidence and should be used cautiously in humans (102).
C. **Martin's Rule:** In Martin's analysis of bioavailability data of 553 compounds in rats, he proposed a simple scoring scheme called ABS. Martin predicts rat bioavailability from many molecular properties like PSA Lipinski's rule of five and molecular charged state (103). Since Martin's rule was developed using data gotten from rats, extrapolation of the performance in humans also needs further investigation.

Quantitative Models

The need for quantitative models to predict biological membrane permeability of drug candidates has gained relevance due to established drawbacks stemming from the sole use of qualitative models such as Lipinski's Rule of Five. As a result, quantitative models are developed by correlating experimentally derived permeability and computed molecular descriptors of drug-like compounds. Figure 4 illustrates 2D and 3D molecular structures, conformational space, and wave function for predicting membrane permeability of candidate compounds with the corresponding molecular descriptors. These descriptors refer to the mathematical representation of properties of molecules obtained from algorithms (104). They can perform similarity searches in molecular libraries by finding molecules with similar chemical and physical properties due to their similar descriptors' data. The numerical values of the molecular descriptors allow the quantitative description of the physical and chemical information of the molecules. For instance, log *P* quantitatively represents the molecules' lipophilicity. It is obtained by determining the molecule's partitioning in the aqueous-lipophilic phases (e.g. water/n-octanol) interface (105). In addition, these descriptors are applied in adsorption, distribution, metabolism, excretion, and toxicity (ADMET) prediction models, correlating the structure-property relationship to simulate ADMET properties of compounds based on their descriptors values (106). The 2D and 3D molecular descriptors are applicable depending on the molecular representation level needed for estimating the descriptor. Although a 1D descriptor is also used, it is the simplest, representing the information obtained from the formula of the molecule, including the molecular weight, atom type, and count contained in the molecules. More complex than the former is the 2D, representing the molecule's information, including shape, size, and electronic configuration, subject to the database volume (106).

Hence, the calculation of a molecule's part, missing in the data, could produce a false result. Lastly, the 3D molecular descriptors predict the properties-relating of the molecular 3D conformation like intra-molecular H-bonding (104). Examples of 3D calculation descriptors of the molecules are the polar and non-polar surface area. This correlation is usually obtained through methods from simple statistical analysis (such as linear regression analysis and principal component analysis) (107) to complex methods (usually involving artificial neural networks (ANN), support vector machines (SVM), and genetic algorithms (GA) (108–111). These complex methods were utilized in various models, including the Andrew model, Yoshida model, Pintore model (112), Turner and Maddalena model (113), Wang model (110), Moda model (114), and Ma model (111). Molecular descriptors gleaned from fragment and atom counts that have been correlated with membrane permeability with varying success include hydrogen bonding capacity, lipophilicity, and molecular size. Other descriptors include electro-topological state indexes, a combined ensemble of physico-chemical properties, and solubility parameters. Evidence suggests that extrapolations on membrane permeability using simple methods extensively are similar to those obtained from more complex computational methods (115,116).

In contrast with the simple model, which applies a few descriptors, most previously reported models for predictive permeability values use several structural parameters and complex equations. For easy prediction, a simple method for membrane permeability is a necessity. A reported case study

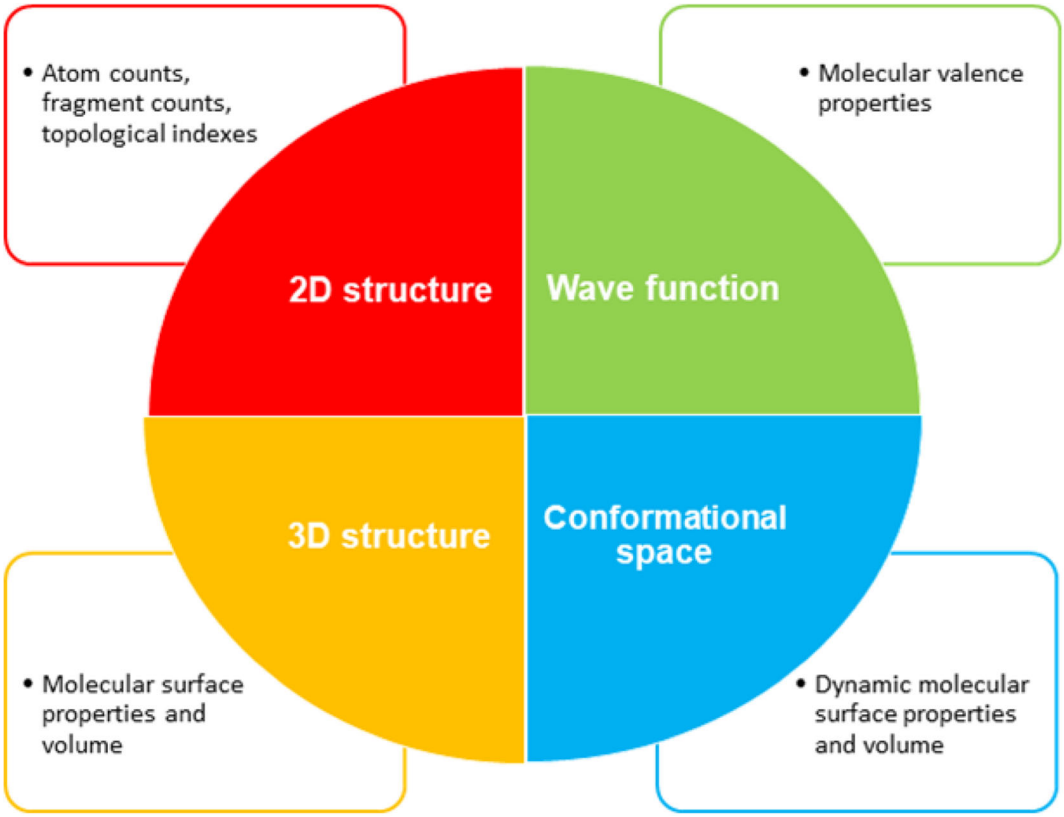

Fig. 4. A schematic representation of molecular structure representations (2D structure, 3D structures, conformational space, and wave function) for predicting membrane permeability of candidate compounds with the corresponding molecular descriptors that can be derived from them.

showed that Caco-2 cell permeability was predicted using a data set of selected compounds (50) for training an ANN model. The model produced an r^2 value of 0.952, which correlated with reported experimental log *kp* values, indicating a complex relationship between the permeability and the penetrant (117). Similarly, a simple ANN method, which did not use experimental parameters, was developed and used to predict famotidine permeability. The simple predictor produces a similar precise permeability prediction for new drugs compared to the complex equations model (117).

The solvation energy (118), solubility (119), and lipophilicity (118,119), have been described using molecular surface properties obtained from molecular mechanics calculations. Polar molecular surface area (PSA), assumed to be related to hydrogen bonding capacity, has gained increased relevance as a molecular surface property in predicting the rate of passive membrane transport due to its ability to predict membrane permeability more accurately (107,120–127). A modification of the PSA method known as dynamic PSA (PSA_d), which considers low energy conformations and single molecular conformation obtained from the usual PSA method, has also been observed to show conformational flexibility of compounds better. Though most studies demonstrating the importance of the PSA method were done with compounds with low PSA values, more conformationally flexible compounds with larger PSA values are expected to display substantial variability between PSA and PSA_d.

The methods for predicting human intestinal permeability include a model constructed using PSA, lipophilicity, and hydrogen bonding properties of compounds based on partial least squares projections (PLS) (124). Another method for predicting intestinal permeability from 3D structure–based molecular descriptors is a molecular surface-weighted holistic invariant molecular method (MS-WHIM) (128). The MS-WHIM model transcribes information encoded by the compound's 3D molecular structure into descriptors related to physicochemical properties. Instead of using molecular descriptors, another method correlates vectors that express information relating to surface properties of molecules (called molecular "hashkeys") with intestinal absorption through a neural network (129).

Molecular simulation models have been applied to characterize small and drug interactions with membranes in many decades (130). Some simulations of solute like benzene in 1,2-dimyristoyl-sn-glycerol-3-phosphocholine (DMPC) revealed the non-heterogeneity of the membrane surrounding. According to the authors, benzene diffuses through the hopping mechanism in the simulation on a single nanosecond. Orsi *et al*. reported the parallel and perpendicular diffusion asymmetry for the motion of the β-blockers in the DMPC lipid bilayer (131). In addition, Marrink and Berendson calculated the permeation rate of water through phospholipid bilayer using the indirect molecular dynamics method (132).

Moreover, a coarse-grained approach of drug and lipid has been used to explore the concentration-dependent effects (130). The report showed that the drug at high concentrations

diffuses from maxima to maxima at a slower rate than the drug at lower concentrations due to the lower concentrations to the increase in partitioning at the bilayer centre. This model representation of the bilayer together with all-atom simulations of the drug allows is characterized by increase sampling time and length scales. A coarse-grained model has been used to simulate drugs such as anticancer (paclitaxel) at higher concentrations to obtain the free energy profile and an anaesthetic drug (halothane) (130). Coarse-grained simulations can be used to characterize the diffusion and drug aggregation of buckyballs in phospholipid bilayers. Spontaneously, the rate of solute permeation across the membranes was reported to be relatively slow. However, advanced molecular dynamics sampling techniques have been reported to assess the free energy across the membrane. Such sampling techniques in MD include metadynamics, thermodynamic integration, and adaptive biasing force (ABF) calculations. These methods have been applied practically to assess the potential of mean force or interactions between the membrane and compounds. An example is illustrated in Fig. 5 (130), in which Jambeck *et al.* reported the application of well-tempered metadynamics, probing the free energy surface of ibuprofen, diclofenac, and aspirin. The report showed that cis and trans ibuprofen conformations lead to dissimilar barriers to cross the membrane.

Though many computational models have been proposed and developed to predict membrane permeability and absorption of drug-like compounds, most quantitative models proposed possess the limitation of being developed using predominantly small datasets, making the compounds used lack structural diversity. Despite the improved performance of complex models involving quantum mechanics compared to simpler models based on fragment counts or atoms, consistency in patterns remains challenging. A conclusion relating to the most accurate prediction of membrane permeability by any of the proposed models is challenging to achieve; instead, the choice of model to adopt rests on the nature of information needed and the complexity of computational effort required.

Formulation Models of Dissolution Study and Disintegration

Computational methods are now employed in predicting drug solubility properties through some thermodynamic calculation and prediction. Virtual screening of soluble-related processes in drug formulation, including dissolution and precipitation, is now estimated using the classical molecular simulation model for free solvation energies (133,134). Computational techniques have as well been applied to solubilization and supersaturation.

Comparatively, several simulation modules have been used in drug dissolution, solubility research in drug development. Finally, some of the essential tools used in drug discovery were discussed and the pharmacophoric models used in discovering lead compounds.

Dose Dissolution and Disintegration Software (DDDPlus)

This computational tool is used in studying the disintegration and dissolution pattern of the primary active ingredient in the dosage form of drug compounds. DDDPlus is an advanced computer program formulated by scientists to simulate the dissolution and disintegration of active pharmaceutical compound ingredients (API) *in vivo*. The software provides adequate information on drug compounds' dissolution and disintegration properties useable in drug formulation design (135), and considers the physicochemical properties of drug formulation ingredients such as pKa, diffusion coefficient, density, and solubility. In addition, it calculates the fluid velocity of the drugs with a micelle-facilitated dissolution through the incorporation of surfactants in the media.

GastroPlus™

GastroPlus™ is another software designed to support biowaiver for different drugs, mainly within class III of BCS. An example of such drugs includes cimetidine and amoxicillin (136). GastroPlus™ is designed to simulate intravenous, ocular, and oral properties in human and animal samples. The software can simulate the pharmacokinetics and pharmacodynamics profiles of a drug. It is used in transporter-based drug-to-drug interaction. The simulation software is modelled to predict drug compounds' absorption and pharmacokinetic process based on the oral properties in human and animal models. The simulation process comprises approximately 90 differential equations encompassing the physical stages during drug transport, such as dissolution, absorption, hepatic metabolism, excretion, and other clearance mechanisms (137). Gastroplus™ was employed in predicting the effect on food using the generic and the reference compound formulation in class II drugs. It was predicted that the food had about 10% prediction error (138).

SimCyp® Simulator Software

SimCyp® simulator software is a population-based ADMET program with a database for mechanistic modelling and simulation of different drug formulation processes such as oral absorption, distribution, drug phase metabolism, and excretion for healthy and disease state populations a distinctive ability also to predict drug-drug interaction (139). The simulator combines all the experimental data from a population-based sample consisting of properties such as demographics, the physiological and genetic information of different sample populations during the pre-clinical phase of drug discovery and development from *in vitro* analysis of enzymes and cellular system with its pertinent physical and chemical properties of the target drug candidate to predict the *in vivo* pharmacokinetic parameters. Several studies have been done using the SimCyp® software; a good example is a study on the effect of proton pump inhibitor on prasugrel HCl product bioequivalence by Fan *et al.* (140).

Non-linear Mixed-Effect Modelling (NONMEM®)

Non-linear mixed-effects modelling is an integrated software tool used in population PK or pharmacodynamics analysis (141). The simulation model platform of NONMEM® is used in studying the bioequivalence of single and multiple-dose administration, thereby predicting the C_{max} and steady-state concentration of drugs. However, reports showed that the single-dose administration simulation resulted in a highly significant result but could show low

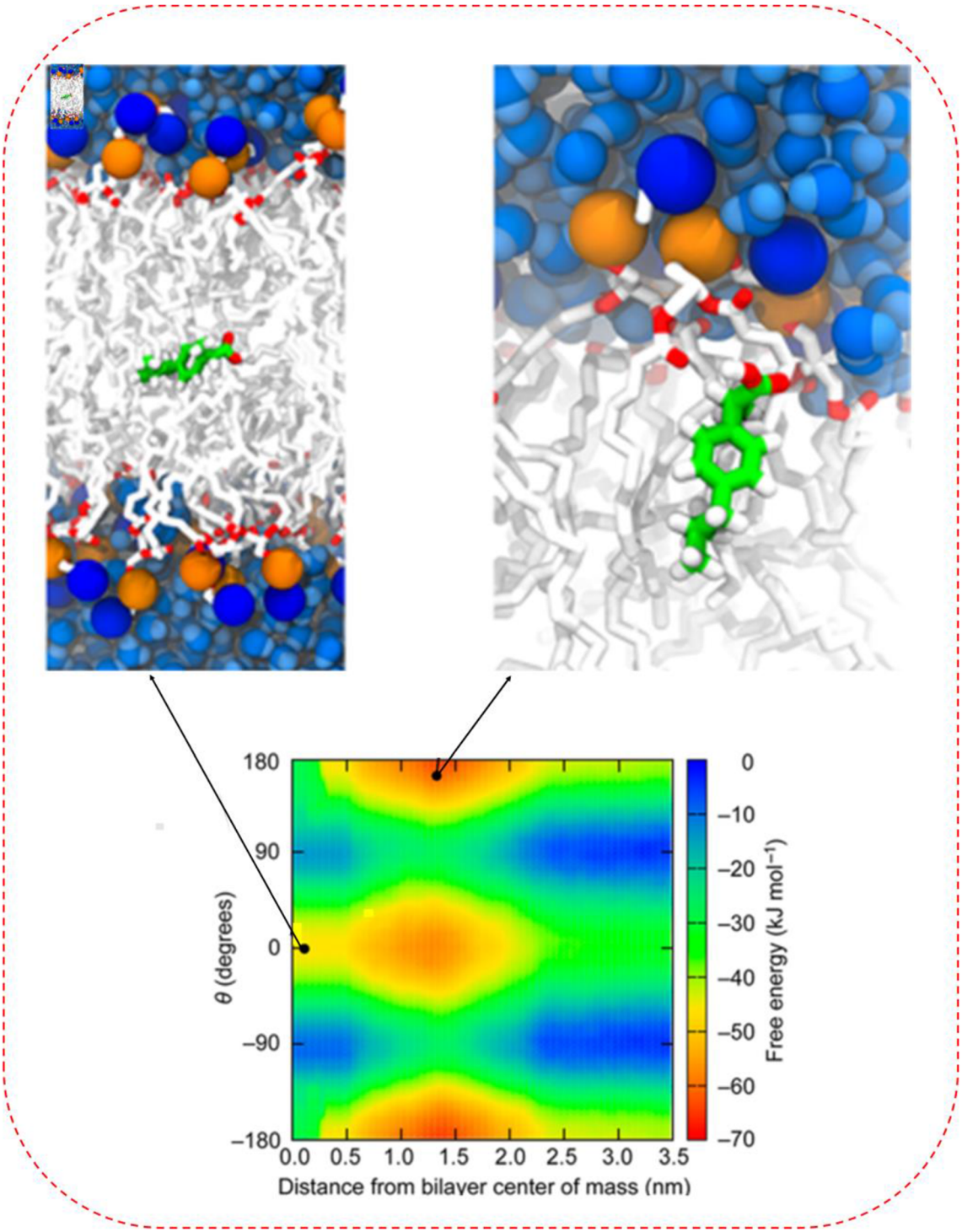

Fig. 5. The illustration of ibuprofen free energy within a sampled bilayer and incorporated well-tempered metadynamics model (130).

sensitivity in predicting the failure in bioequivalence study for steady-state concentrations (142)

Chemoinformatic and Mathematical Predictions of Drug Bioavailability

Until the twentieth century, pharmaceutical research for biologically induced drugs has been a herculean task requiring time, money, and many skills (143). Before a drug can be validated to induce a biological effect, it must have undergone several tests and stages, such as clinical and preclinical trials (144). However, from the inception of computational studies in drug discovery (145), drug discovery and design research have sky-rocketed into a phase of ease and accurate precession. In a study by Agoni *et al.*, the validity and reliability of computational tools are reviewed (146).

The low bioavailability of oral drugs is one major bugbear to the pharmaceutical industry today (128,129). The report states that 10% of oral drug debacle in drug development results from adverse absorption, distribution, metabolism, and excretion properties (147). For this course, research is carried out to access drug candidates' oral pharmacokinetics before moving forward to drug development. The *in vitro* assay is less cost-effective than *in vivo*; however, it cannot capture a typical *in vivo* oral absorption process.

Prediction of oral bioavailability takes its root from Lipinski's rule of five and other attempts for the descriptive method of defining drug-like molecules. Other rules include Veber rule (101, 102), Martin's rule (103), Andrew's model (148), Yoshida's model (149), Turner and Glass model (113), Pintore's model (112), Turner and Maddalena's model (113), and Wang's Model (110). However, these rules attempt to be qualitative rather than quantitative (150,151).

Chemoinformatics Prediction Model

Quantitative Structure-Activity Relationship (QSAR) models were first discovered by Hirono *et al.* using the fuzzy adaptive least square methods. This method classified molecules of 188 non-congeneric into three groups: (1) aromatic, (2) non-aromatic, (3) hetero-aromatic based on the presence of rings (152). The result gave insight into factors affecting bioavailability and its prediction. However, the model was considered impoverished and discrete, and structural fragments were incorporated with indicator variables to increase efficiency (152). More models continue to be developed for predicting oral bioavailability. One of such was built by Yoshida and Topliss (149). This quantitative in silico model used the ordered multi-categorical classification method using the simplex technique method (ORMUCS). This method, although not readily reproducible yet similar results have been obtained using SIMCA (114). Equation (1) explains the discriminant function of ORMUCS, where X_i is the ith component of X which represents the pattern vector in the δ-dimensional measurement space. W_i represents the component's weight assigned. Meanwhile, W denotes the vector's weight.

$$S(x) = WX = \sum_{i=1}^{d} w_i w_j \tag{1}$$

One advantage posed by the QSAR model is that factors that affect bioavailability are examined, and its effect is understood. This transparency is needed for further analyses for bioavailability data with more future work (149). However, there remains a limitation to this model. Compounds with a > 500 MW and high hydrogen bonds were not covered in the dataset used to develop this model. Hence, it might not give the same expected result (149).

In a research study by Moda *et al.*, a hologram QSAR model was designed to experiment with about 250 structurally diverse molecules. The result was analyzed side by side with an external set of 52 molecules, and an excellent result was obtained relatively to the experimented values. This consistency can further be examined for new drug candidates possessing oral bioavailability (114). A case study is a linear quantitative structure-activity relationship (QSAR) model used to model and predict interleukin-1 receptor-associated kinase 4, IRAK-4) inhibition activity of amides and imidazo[1,2-α] pyridines.

Mathematical Prediction

Mathematical or physiologically based pharmacokinetic (PBPK) models have been developed to mimic biological processes. The models use several differential equations to predict bioavailability. Studies show that these models are dynamic and mechanical and are used to determine the variation in patients concerning oral bioavailability. Since 1937, PBPK models have continued to gain ground in their use in drug design research. PK properties, known as ADME (absorption, distribution, metabolism and excretion), are the subject of observation and analysis in oral bioavailability, and alterations in these therapeutic concentrations raise the research alarm. Too low concentrations could mean an ineffective therapy, and too high indicates toxicity. The combination of *in vitro* and *in silico* assay can aid the computation of ADME information input, characterizing the PBPK models (143).

Initial instances of these mathematical methods as of the 1970s were based on solubility and permeability and could only predict the extent of absorption under "static" conditions. These early mathematical models are the absorption potential (AP) and the maximum absorption dose (MAD) Equation. While the former calculates the absorbed portion of a given dose, the latter, on the other hand, calculates the portion absorbed within 6-h time frame (153–155). Although effective, these models could not compute complex phenomena, such as food effects and PH-dependent oral absorption. Table I provides two contrasting information between PK modelling and PBPK approaches. *PBPK Methodology.* PBPK models work by using a set of differential equations to mimic various compartments within the body with the sole aim of articulating the fate of substance (in this case, drugs) in the body. Organs and tissues with similar blood perfusion rates are usually grouped into the same compartment. In order words, organs such as the intestinal tract, skin, lungs, anus, lungs, and others can be grouped as entry portals, while kidney, liver, and others are classified as exit portals (156).

Figure 6 shows the various compartment that represents the organs and tissues. The rate of blood through these compartments depends on the tissue volume and the species of interest. Therefore, in developing a PBPK model, it is vital to consider the physiological and anatomical data of the

Table I. A Contrast Between the PK Modelling and PBPK Approach

S/N	Classical Pk modelling	PBPK approach
1	Based on PK data	Based on physiological knowledge
2	Result is a set of fit parameters	Result is a predictive simulation

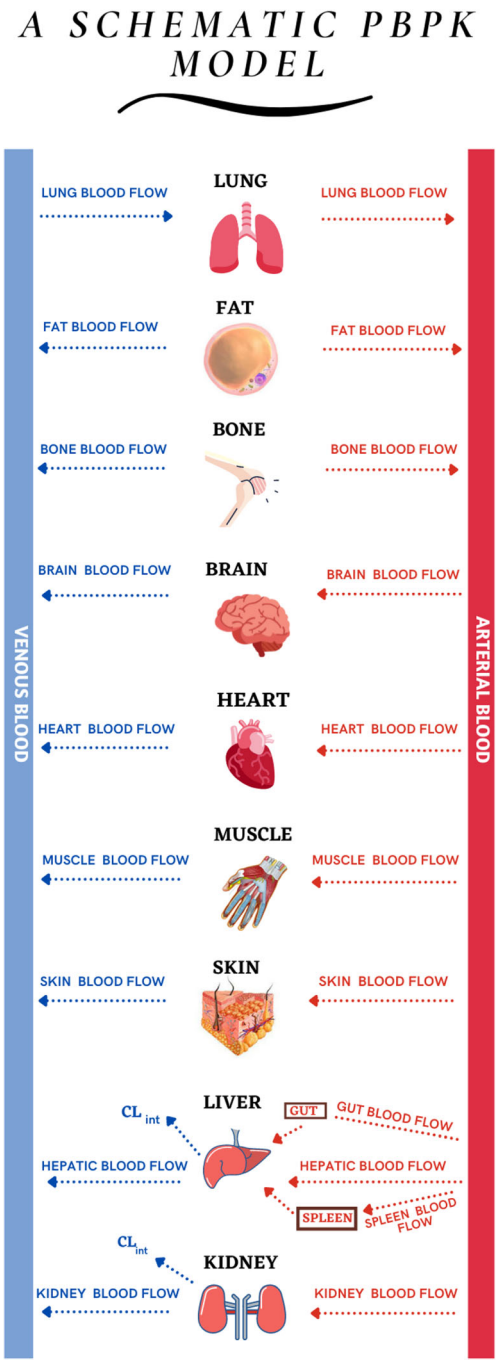

Fig. 6. A schematic representation of a PBPK model (Designed: Yinka Akinsiku, 2021)

specific species required and the compound's partition coefficient (PCs) in different tissues (157). There is either a result based on the permeability-limited rate or the perfusion-limited process for each tissue. The permeability-limited rate comes to play when dealing with hydrophilic or large molecules. In this case, the limiting process of absorption is based on the permeability rate across cellular membranes. In contrast, the perfusion-limited process occurs with small lipophilic molecules where the limiting process of absorption across the cellular membrane is the blood flow to the tissues (157).

The differential equations used to model the PBPK model can be described as follows:

$$VT \times dCT/dt = Q_T(\, C_A - CV_T) \tag{2}$$

$$CV_T = {}^{C_T}/_{(K_P/B:P)} \tag{3}$$

Equations (2) and (3) represent the principles followed for non-eliminating tissues. Thus, Q represents the blood flow (L/h), C is concentration in mg/L, V for the volume, T denotes tissues, A for arterial, venous is denoted by V, and VT is the tissue volume.

Equation (4) represents the principle implemented for eliminating tissues.

$$VT \times \frac{dCT}{dt} = Q_T\,(C_A - CV_T) - CL_{int} \times CV_U T \tag{4}$$

where CL_{int} represents the intrinsic clearance of the compound (L/h), and the u-term is unbound.

Applications of PBPK Models in Drug Research. Throughout the drug discovery process and development, PBPK models are habitually applied (156). For instance, it is interesting to note that current research aims to develop PBPK models for nanomaterials (NMs). Although it is challenging, however, it is progressive. For example, one PBPK model was developed to eliminate the biodistribution of NMs (158), and another was developed from existing toxicodynamic compartment models that predict the quantity of Ag and carbon NPs inhaled in the lungs (159). In addition, PBPK model application is associated with drugs with a narrow therapeutic window, such as in pregnancy and organ transplant populations (160).

CONCLUSION

Although the therapeutic drug efficacy might be unattainable due to the low fraction of an administered dose of the unchanged drug that reaches the systemic circulation, various interfacing techniques provide a potential platform to discover a potential novel method or design a drug that can avert BA issues. Experimental techniques have proven results in bioavailability studies despite their shortcomings. Similarly, computational modelling approaches have been evolving from providing mechanistic insights into the oral drug delivery system simulation to predicting and providing unravelling the properties involved in gastrointestinal tract (GIT) drug absorption. Such models can be classified as qualitative and quantitative such as Rule-of-Five, Verber's Rule, Martin's Rule, and Polar molecular surface area (PSA), which relate to hydrogen bonding capacity. The relevance of PSA, a molecular surface property, is increasingly helpful in predicting the rate of passive membrane transport due to its

ability to predict membrane permeability. Several descriptors and the response of interest include solubility, permeability, and interactions with the transport protein. The *in vivo* and *in vitro* experimental models have been used to predict drug candidates' permeability. Recently, computational models were employed to predict passive intestinal membrane permeability, which conveniently reduces the time for hit compounds to follow the developmental process into the fourth clinical stage. Similar computational models and multivariate tools predict drugs' permeability. Computational methods are now employed in predicting drug solubility properties through some thermodynamic calculations and prediction. Using the classical molecular simulation model for free solvation energies, virtual screening of soluble-related processes in drug formulation is estimable. Conclusively, considering the application of the in silico-experimental interface provides a critical avenue to explore the possibility of a lasting solution to drug BA problems, especially poor aqueous solubility, low dissolution rate, poor permeation, and extreme drug metabolism in the liver.

DECLARATIONS

Ethical Approval This article does not contain any studies with human participants or animals performed by any authors.

Research Involving Human Participants and Animals and Informed Consent This study did not require informed consent since it is a review article that requires no human participant studies performed by any of the authors.

Conflict of Interest The authors declare no competing interests.

REFERENCES

1. Preziosi P. Faster drug approval: challenges for safety. Expert Opin Drug Saf. 2016;15:1205–18.
2. Abed I. The approval process of medicines in Europe. Med Writ. 2014;23:117–21.
3. Savjani KT, Gajjar AK, Savjani JK. Drug solubility: importance and enhancement techniques. ISRN Pharm. 2012;2012:1–10.
4. Kok-Yong S, & Lawrence L. Drug distribution and drug elimination. Basic Pharmacokinetic Concepts and Some Clinical Applications (2015). https://doi.org/10.5772/59929.
5. Drenth-van Maanen AC, Wilting I, Jansen PAF. Prescribing medicines to older people—how to consider the impact of ageing on human organ and body functions. Br J Clin Pharmacol. 2020;86:1921–30.
6. Coltescu AR, Butnariu M, Sarac I. The importance of solubility for new drug molecules. Biomed Pharmacol J. 2020;13:577–83.
7. Chavda P. Vivek., S. M. Biological classification system (BCS); with a New Perspective. MOJ Bioequivalence & Bioavailability. 2017;3:108–9.
8. Homayun B, Lin X, Choi HJ. Challenges and recent progress in oral drug delivery systems for biopharmaceuticals. Pharmaceutics. 2019;11:129.
9. Currie GM. Pharmacology, part 2: Introduction to pharmacokinetics. J Nucl Med Technol. 2018;46:221–30.
10. Andrysek T. Impact of physical properties of formulations on bioavailability of active substance: current and novel drugs with cyclosporine. Mol Immunol. 2003;39:1061–5.
11. Stillhart C, et al. Impact of gastrointestinal physiology on drug absorption in special populations—An UNGAP review. Eur J Pharm Sci. 2020;147:105280. https://doi.org/10.1016/j.ejps.2020.105280.
12. Elbarbry F. Oral Bioavailability in special populations. MOJ Bioequivalence Bioavailab. 2015;1:49–52.
13. Ruiz, María Esperanza ., Montoto, S. S. Routes of drug administration. Cardiac Arrest: The Science and Practice of Resuscitation Medicine (2018). https://doi.org/10.1007/978-3-319-99593-9_6 97.
14. Genser D. Food and drug interaction: consequences for the nutrition/health status. Ann Nutr Metab. 2008;52:29–32.
15. Koziolek M, et al. The mechanisms of pharmacokinetic food-drug interactions – a perspective from the UNGAP group. Eur J Pharm Sci. 2019;134:31–59.
16. FDA. Guidance for Industry. Bioavailability and bioequivalence studies submitted in NDAs or INDs—general considerations. Center for Drug Evaluation and Research (CDER) http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm Phone: (2014).
17. Lynch T, Price A. The effect of cytochrome P450 metabolism on drug response, interactions, and adverse effects. Am Fam Physician. 2007;76:391–6.
18. Singh V, Sharma PK, Alam MA. Metabolism of drugs with inhibition of enzymes. J Drug Metab Toxicol. 2018;09:1–6.
19. Li H, et al. Biomimetic synthesis of proline-derivative templated mesoporous silica for increasing the brain distribution of diazepam and improving the pharmacodynamics of nimesulide. Drug Deliv. 2017;24:1086–98.
20. Zhang Y, Wang J, Bai X, Jiang T. Mesoporous silica nanoparticles for increasing the oral bioavailability and permeation of poorly water soluble drugs. Mol Pharm. 2012;9:505–13.
21. Sharma M, Sharma R, Jain DK. Nanotechnology based approaches for enhancing oral bioavailability of poorly water soluble antihypertensive drugs. Scientifica (Cairo). 2016;2016(1–11).
22. Danish KA, Lubhan S. Various techniques of bioavailability enhancement: a review. J Drug Deliv Ther. 2016;6:34–41.
23. Ansari MJ. An overview of techniques for multifold enhancement in solubility of poorly soluble drugs. Curr Issues Pharm Med Sci. 2019;32:203–9.
24. Pathak K, Raghuvanshi S. Oral bioavailability: issues and solutions via nanoformulations. Clin Pharmacokinet. 2015;54:325–57.
25. Ndlovu ST, et al. Domperidone nanocrystals with boosted oral bioavailability: fabrication, evaluation and molecular insight into the polymer-domperidone nanocrystal interaction. Drug Deliv Transl Res. 2019;9:284–97.
26. Budiman A. Characterization of drugs encapsulated into mesoporous silica. Int J Appl Pharm. 2019;11:7–11.
27. Fridgeirsdottir GA, Harris R, Fischer PM, Roberts CJ. Support tools in formulation development for poorly soluble drugs. J Pharm Sci. 2016;105:2260–9.
28. Mitrović JR, et al. Nanocrystal dispersion of DK-I-56–1, a poorly soluble pyrazoloquinolinone positive modulator of α6 GABAA receptors: formulation approach toward improved in vivo performance. Eur J Pharm Sci. 2020;152:105432.
29. Gigliobianco, Maria Rosa., Casadidio, Cristina., Censi Roberta. Martino, P. Di. Nanocrystals of poorly soluble drugs: drug bioavailability and physicochemical stability. Pharmaceutics 10, 1–29 (2018).
30. Gomez-Orellana I. Strategies to improve oral drug bioavailability. Expert Opin Drug Deliv. 2005;2:419–33.
31. Mitragotri S, Burke PA, Langer R. Overcoming the challenges in administering biopharmaceuticals: formulation and delivery strategies. Nat Rev Drug Discov. 2014;13:655–72.
32. Sharif BA. Nanotechnology approaches for oral bioavailability enhancement of drugs undergoing extensive hepatic first pass metabolism. Drug Des Open Access. 2018;07:46.
33. Padhi S, Kumar A, Behera A. Biomedicine & Pharmacotherapy Type II diabetes mellitus : a review on recent drug based therapeutics. Biomed Pharmacother. 2020;131:1–23.
34. Schultz HB, Meola TR, Thomas N, Prestidge CA. Oral formulation strategies to improve the bioavailability and

mitigate the food effect of abiraterone acetate. Int J Pharm. 2020;577:1–12.
35. Baghel P, Roy A, Verma S, Satapathy T, Bahadur S. Amelioration of lipophilic compounds in regards to bioavailability as self-emulsifying drug delivery system (SEDDS). Futur J Pharm Sci. 2020;6:1–11.
36. Hui Z, Kumar A, Wan P, Heng S. Overview of milling techniques for improving the solubility of poorly water-soluble drugs. Asian J Pharm Sci. 2015;10:255–74.
37. Gupta S, Kesarla R, Omri A. Formulation strategies to improve the bioavailability of poorly absorbed drugs with special emphasis on self-emulsifying systems. ISRN Pharm. 2013;2013:1–16.
38. Yousef MAE, Vangala VR. Pharmaceutical cocrystals: molecules, crystals, formulations, medicines. Cryst Growth Des. 2019;19:7420–38.
39. Kudo S, Takiyama H. Production method of carbamazepine/saccharin cocrystal particles by using two solution mixing based on the ternary phase diagram. J Cryst Growth. 2014;392:87–91.
40. Arenas-García JI, Herrera-Ruiz D, Mondragón-Vásquez K, Morales-Rojas H, Höpfl H. Co-crystals of active pharmaceutical ingredients-acetazolamide. Cryst Growth Des. 2010;10:3732–42.
41. Guo C, et al. Drug-drug cocrystals provide significant improvements of drug properties in treatment with progesterone. Cryst Growth Des. 2020;20:3053–63.
42. Wang X, et al. Drug-drug cocrystals: opportunities and challenges. Asian J Pharm Sci. 2020;2:1–12.
43. Wiedmann TS, Naqwi A. Pharmaceutical salts: theory, use in solid dosage forms and in situ preparation in an aerosol. Asian J Pharm Sci. 2016;11:722–34.
44. Rautio J, Meanwell NA, Di L, Hageman MJ. The expanding role of prodrugs in contemporary drug design and development. Nat Rev Drug Discov. 2018;17:559–87.
45. Jain R, Majumdar S, Nashed Y, Pal D, Mitra AK. Circumventing P-glycoprotein-mediated cellular efflux of quinidine by prodrug derivatization. Mol Pharm. 2004;1:290–9.
46. Zhang X, Xing H, Zhao Y, Ma Z. Pharmaceutical dispersion techniques for dissolution and bioavailability enhancement of poorly water-soluble drugs. Pharmaceutics. 2018;10:74.
47. Rabinow BE. Nanosuspensions in drug delivery. Nat Rev Drug Discov. 2004;3:785–96.
48. Hadinoto K, Sundaresan A, Cheow WS. Lipid-polymer hybrid nanoparticles as a new generation therapeutic delivery platform: A review. Eur J Pharm Biopharm. 2013;85:427–43.
49. Khan S, De Matas M, Zhang J, Anwar J. Nanocrystal preparation: low-energy precipitation method revisited. Cryst Growth Des. 2013;13:2766–77.
50. Ullah N, et al. Dexibuprofen nanocrystals with improved therapeutic performance: fabrication, characterization, in silico modeling, and in vivo evaluation. Int J Nanomedicine. 2018;13:1677–92.
51. Mathew M, Krishnakumar K, Dineshkumar B, Nair SK. Antibiotics nanosuspension: a review. J Drug Deliv Ther. 2017;7:128–31.
52. Nayak AK, Panigrahi PP. Solubility enhancement of etoricoxib by cosolvency approach. ISRN Phys Chem. 2012;2012:1–5.
53. Seedher N, Kanojia M. Co-solvent solubilization of some poorly-soluble antidiabetic drugs Solubilization antidiabetic drugs. Pharm Dev Technol. 2009;14:185–92.
54. Seo SH, et al. A mixed micellar formulation for the transdermal delivery of an Indirubin analog. Pharmaceutics. 2020;12:1–10.
55. Boyd BJ, et al. Successful oral delivery of poorly water-soluble drugs both depends on the intraluminal behavior of drugs and of appropriate advanced drug delivery systems. Eur J Pharm Sci. 2019;137:104967.
56. Kalepu S, Nekkanti V. Insoluble drug delivery strategies: review of recent advances and business prospects. Acta Pharm Sin B. 2015;5:442–53.
57. Mukherjee A, et al. Lipid-polymer hybrid nanoparticles as a nextgeneration drug delivery platform: state of the art, emerging technologies, and perspectives. Int J Nanomedicine. 2019;14:1937–52.
58. Güven E. Lipid-based nanoparticles in the treatment of erectile dysfunction. Int J Impot Res. 2020;32:578–86.
59. Wakaskar RR. General overview of lipid–polymer hybrid nanoparticles, dendrimers, micelles, liposomes, spongosomes and cubosomes. J Drug Target. 2018;26:311–8.
60. Thakkar H, Patel B, Thakkar S. A review on techniques for oral bioavailability enhancement of drugs. Int J Pharm Sci Rev Res. 2010;4:203–23.
61. Ahn H, Park J. Liposomal delivery systems for intestinal lymphatic drug transport. Biomater Res. 2016;20:1–6.
62. Dressman JB, Thelen K, Jantratid E. Towards quantitative prediction of oral drug absorption. Clin Pharmacokinet. 2008;47:655–67.
63. Norris DA, Leesman GD, Sinko PJ, Grass GM. Development of predictive pharmacokinetic simulation models for drug discovery. J Control Release. 2000;65:55–62.
64. Huang W, Lee SL, Yu LX. Mechanistic approaches to predicting oral drug absorption. AAPS J. 2009;11:217–24.
65. Kaur N, Narang A, Bansal AK. Use of biorelevant dissolution and PBPK modeling to predict oral drug absorption. Eur J Pharm Biopharm. 2018;129:222–46.
66. Willmann S, Edginton AN, Dressman JB. Development and validation of a physiology-based model for the prediction of oral absorption in monkeys. Pharm Res. 2007;24:1275–82.
67. Ni PF, Ho NFH, Fox JL, Leuenberger H, Higuchi WI. Theoretical model studies of intestinal drug absorption V. Non-steady-state fluid flow and absorption. Int J Pharm. 1980;5:33–47.
68. Kannan R, Przekwas A. A multiscale absorption and transit model for oral drug delivery: formulation and applications during fasting conditions. Int J Numer Method Biomed Eng. 2020;36:1–20.
69. Yu LX, Lipka E, Crison JR, Amidon GL. Transport approaches to the biopharmaceutical design of oral drug delivery systems: prediction of intestinal absorption. Adv Drug Deliv Rev. 1996;19:359–76.
70. Yu LX, Amidon GL. Estimating oral drug absorption. Int J Pharm. 1999;186:119–25.
71. Agoram B, Woltosz WS, Bolger MB. Predicting the impact of physiological and biochemical processes on oral drug bioavailability. Adv Drug Deliv Rev. 2001;50.
72. Darwich SA, Neuhoff S, Jamei M, Rostami-Hodjegan. A. Interplay of metabolism and transport in determining oral drug absorption and gut wall metabolism: a simulation assessment using the "Advanced Dissolution, Absorption, Metabolism (ADAM)" model. Curr Drug Metab. 2011;11:716–29.
73. Eissing T, et al. A computational systems biology software platform for multiscale modeling and simulation: integrating whole-body physiology, disease biology, and molecular reaction networks. Front Physiol. 2011;FEB:1–10.
74. Norinder U, Bergström CAS. Prediction of ADMET properties. ChemMedChem. 2006;1:920–37.
75. Glassey J. Multivariate data analysis for advancing the interpretation of bioprocess measurement and monitoring data. Adv Biochem Eng Biotechnol. 2013;132:167–91.
76. Bergström CAS, Charman WN, Porter CJH. Computational prediction of formulation strategies for beyond-rule-of-5 compounds. Adv Drug Deliv Rev. 2016;101:6–21.
77. Bergström CAS, Wassvik CM, Norinder U, Luthman K, Artursson P. Global and local computational models for aqueous solubility prediction of drug-like molecules. J Chem Inf Comput Sci. 2004;44:1477–88.
78. Palmer DS, Mitchell JBO. Is experimental data quality the limiting factor in predicting the aqueous solubility of druglike molecules? Mol Pharm. 2014;11:2962–72.
79. Bergström CAS, Wassvik CM, Johansson K, Hubatsch I. Poorly soluble marketed drugs display solvation limited solubility. J Med Chem. 2007;50:5858–62.
80. Wassvik CM, Holmén AG, Draheim R, Artursson P, Bergström CAS. Molecular characteristics for solid-state limited solubility. J Med Chem. 2008;51:3035–9.
81. Bergström CAS, et al. Early pharmaceutical profiling to predict oral drug absorption: Current status and unmet needs. Eur J Pharm Sci. 2014;57:173–99.

82. Diakidou A, et al. Characterization of the contents of ascending colon to which drugs are exposed after oral administration to healthy adults. Pharm Res. 2009;26:2141–51.
83. Reppas C, Karatza E, Goumas C, Markopoulos C, Vertzoni M. Characterization of contents of distal ileum and cecum to which drugs/drug products are exposed during bioavailability/bioequivalence studies in healthy adults. Pharm Res. 2015;32:3338–49.
84. Kossena GA, et al. Low dose lipid formulations: effects on gastric emptying and biliary secretion. Pharm Res. 2007;24:2084–96.
85. Fagerberg JH, Karlsson E, Ulander J, Hanisch G, Bergström CAS. Computational prediction of drug solubility in fasted simulated and aspirated human intestinal fluid. Pharm Res. 2015;32:578–89.
86. Bergström CAS, Larsson P. Computational prediction of drug solubility in water-based systems: qualitative and quantitative approaches used in the current drug discovery and development setting. Int J Pharm. 2018;540:185–93.
87. Lüder K, Lindfors L, Westergren J, Nordholm S, Kjellander R. In silico prediction of drug solubility. 3. Free energy of solvation in pure amorphous matter. J Phys Chem B. 2007;111:7303–11.
88. Westergren J, et al. In silico prediction of drug solubility: 1. Free energy of hydration. J Phys Chem B. 2007;111:1872–82.
89. Newby D, Freitas AA, Ghafourian T. Decision trees to characterise the roles of permeability and solubility on the prediction of oral absorption. Eur J Med Chem. 2015;90:751–65.
90. Palm K, et al. Evaluation of dynamic polar molecular surface area as predictor of drug absorption: comparison with other computational and experimental predictors. J Med Chem. 1998;41:5382–92.
91. Camenisch G, Alsenz J, Van De Waterbeemd H, Folkers G. Estimation of permeability by passive diffusion through Caco-2 cell monolayers using the drugs' lipophilicity and molecular weight. Eur J Pharm Sci. 1998;6:313–9.
92. Matsson P, Doak BC, Over B, Kihlberg J. Cell permeability beyond the rule of 5. Adv Drug Deliv Rev. 2016;101:42–61.
93. Mateus A, Matsson P, Artursson P. Rapid measurement of intracellular unbound drug concentrations. Mol Pharm. 2013;10:2467–78.
94. Yabe Y, Galetin A, Houston JB. Kinetic characterization of rat hepatic uptake of 16 actively transported drugs. Drug Metab Dispos. 2011;39:1808–14.
95. Palmer DS, Mišin M, Fedorov MV, Llinas A. Fast and general method to predict the physicochemical properties of druglike molecules using the integral equation theory of molecular liquids. Mol Pharm. 2015;12:3420–32.
96. Walters WP, Murcko MA. Can we learn to distinguish between drug-like and nondrug-like molecules. JMedChem. 1998;2623(1998):3314–24.
97. Sadowski J, Kubinyi H. A scoring scheme for discriminating between drugs and nondrugs. J Med Chem. 1998;41:3325–9.
98. Gillet VJ, Willett P, Bradshaw J. Identification of biological activity profiles using substructural analysis and genetic algorithms. J Chem Inf Comput Sci. 1998;38:165–79.
99. Wagener M, van Geerestein VJ. Potential drugs and nondrugs: prediction and identification of important structural features. J Chem Inf Comput Sci. 2000;40:280–92.
100. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv Drug Deliv Rev. 2012;64:4–17.
101. Veber DF, et al. Molecular properties that influence the oral bioavailability of drug candidates. J Med Chem. 2002;45:2615–23.
102. Hou T, Wang J, Zhang W, Xu X. ADME evaluation in drug discovery. 7. prediction of oral absorption by correlation and classification. J Chem Inf Model. 2007;47:208–18.
103. Zhu J, Wang J, Yu H, Li Y, Hou T. Recent developments of in silico predictions of oral bioavailability. Comb Chem High Throughput Screen. 2011;14:362–74.
104. Admet, P. *et al.* Computer-aided prediction of pharmacokinetic (ADMET) properties. dosage form design parameters (Elsevier Inc., 2018). https://doi.org/10.1016/B978-0-12-814421-3.00021-X.
105. Balaban, A. T. Drug Design , Molecular descriptors in. 2014; 1–31 https://doi.org/10.1007/978-3-642-27737-5
106. Hong, H. *et al.* Mold2 , Molecular descriptors from 2D structures for chemoinformatics and toxicoinformatics. J Chem Inf Model 48, 1337–1344 (2008).
107. Palm K, Luthman K, Ungell AL, Strandlund G, Artursson P. Correlation of drug absorption with molecular surface properties. J Pharm Sci. 1996;85:32–9.
108. Wessel MD, Jurs PC, Tolan JW, Muskal SM. Prediction of human intestinal absorption of drug compounds from molecular structure. J Chem Inf Comput Sci. 1998;38:726–35.
109. Turner JV, Maddalena DJ, Agatonovic-Kustrin S. Bioavailability prediction based on molecular structure for a diverse series of drugs. Pharm Res. 2004;21:68–82.
110. Wang J, Krudy G, Xie XQ, Wu C, Holland G. Genetic algorithm-optimized QSPR models for bioavailability, protein binding, and urinary excretion. J Chem Inf Model. 2006;46:2674–83.
111. Ma CY, et al. Prediction models of human plasma protein binding rate and oral bioavailability derived by using GA-CG-SVM method. J Pharm Biomed Anal. 2008;47:677–82.
112. Pintore M, Van De Waterbeemd H, Piclin N, Chrétien JR. Prediction of oral bioavailability by adaptive fuzzy partitioning. Eur J Med Chem. 2003;38:427–31.
113. Turner JV, Glass BD, Agatonovic-Kustrin S. Prediction of drug bioavailability based on molecular structure. Anal Chim Acta. 2003;485:89–102.
114. Moda TL, Montanari CA, Andricopulo AD. Hologram QSAR model for the prediction of human oral bioavailability. Bioorg Med Chem. 2007;15:7738–45.
115. Norinder U, Österberg T, Artursson P. Theoretical calculation and prediction of intestinal absorption of drugs in humans using MolSurf parametrization and PLS statistics. Eur J Pharm Sci. 1999;8:49–56.
116. Österberg T, Norinder U. Theoretical calculation and prediction of P-glycoprotein-interacting drugs using MolSurf parametrization and PLS statistics. Eur J Pharm Sci. 2000;10:295–303.
117. Degim Z. Prediction of permeability coefficients of compounds through Caco-2 Cell monolayer using artificial neural network analysis. Drug Dev Ind Pharm. 2005;31:935–42.
118. Ooi T, Oobatake M, Némethy G, Scheraga HA. Accessible surface areas as a measure of the thermodynamic parameters of hydration of peptides. Proc Natl Acad Sci U S A. 1987;84:3086–90.
119. Amidon GL, Yalkowsky SH, Anik ST, Valvani SC. Solubility of nonelectrolytes in polar solvents. V. Estimation of the solubility of aliphatic monofunctional compounds in water using a molecular surface area approach. J Phys Chem. 1975;79:2239–46.
120. Ertl P, Rohde B, Selzer P. Fast calculation of molecular polar surface area as a sum of fragment-based contributions and its application to the prediction of drug transport properties. J Med Chem. 2000;43:3714–7.
121. Kelder J, Grootenhuis PDJ, Bayada DM, Delbressine LPC, Ploemen JP. Polar molecular surface as a dominating determinant for oral absorption and brain penetration of drugs. Pharm Res. 1999;16:1514–9.
122. Sugawara E, Nikaido H. Properties of AdeABC and AdeIJK efflux systems of Acinetobacter baumannii compared with those of the AcrAB-TolC system of Escherichia coli. Antimicrob Agents Chemother. 2014;58:7250–7.
123. Krarup LH, Christensen IT, Hovgaard L, Frokjaer S. Predicting drug absorption from molecular surface properties based on molecular dynamics simulations. Pharm Res. 1998;15:972–8.
124. Winiwarter S, et al. Correlation of human jejunal permeability (in vivo) of drugs with experimentally and theoretically derived parameters. A multivariate data analysis approach. J Med Chem. 1998;41:4939–49.
125. Clark DE. Rapid calculation of polar molecular surface area and its application to the prediction of transport phenomena. 2. Prediction of blood−brain barrier penetration. J Pharm Sci. 1999;88:815–21.

126. Goodwin JT, Mao B, Vidmar TJ, Conradi RA, Burton PS. Strategies toward predicting peptide cellular permeability from computed molecular descriptors. J Pept Res. 1999;53:355–69.
127. Van Waterbeemd, De H, Camenisch G, Folkers G & Raevsky OA Estimation of Caco-2 cell permeability using calculated molecular descriptors. Quantitative Structure-Activity Relationships vol. 15 (1996).
128. Bravi G, Wikel JH. Application of MS-WHIM Descriptors :3. Prediction of molecular properties. Quant Struct Relationships. 2000;19:39–49.
129. Segarra V, López M, Ryder H, Palacios JM. Prediction of drug permeability based on Grid calculations. Quant Struct Relationships. 1999;18:474–81.
130. Loverde SM. Molecular simulation of the transport of drugs across model membranes. J Phys Chem Lett. 2014;5:1659–65.
131. Orsi M, Essex JW. Permeability of drugs and hormones through a lipid bilayer: Insights from dual-resolution molecular dynamics. Soft Matter. 2010;6:3797–808.
132. Marrink SJ, Berendsen HJC. Simulation of water transport through a lipid membrane. J Phys Chem. 1994;98:4155–68.
133. Matos GDR, et al. Approaches for calculating solvation free energies and enthalpies demonstrated with an update of the FreeSolv database. J Chem Eng Data. 2017;62:1559–69.
134. Lundborg M, Lindahl E. Automatic GROMACS topology generation and comparisons of force fields for solvation free energy calculations. J Phys Chem B. 2015;119:810–23.
135. Almukainzi M, Okumu A, Wei H, Löbenberg R. Simulation of in vitro dissolution behavior using DDDPlus™. AAPS PharmSciTech. 2015;16:217–21.
136. Tsume Y, Amidon GL. The biowaiver extension for BCS class III drugs: the effect of dissolution rate on the bioequivalence of BCS class III immediate-release drugs predicted by computer simulation. Mol Pharm. 2010;7:1235–43.
137. Naylor TA, et al. Use of a Gastro-Intestinal Model and GastroPLUS™ for the prediction of in vivo performance. J Appl Ther Res. 2006;6:15–9.
138. Rebeka J, et al. PBPK absorption modeling of food effect and bioequivalence in fed state for two formulations with crystalline and amorphous forms of BCS 2 Class Drug in generic drug development. AAPS PharmSciTech. 2019;20:59.
139. Masoud Jamei, Steve Marciniak, Kairui Feng, Adrian Barnett, Geoffery Tucker, A. R.-H. The Simcyp population-based ADME simulator. Clin Eng Handb; 2004. 114–118 https://doi.org/10.1016/B978-012226570-9/50037-5.
140. Fan J, Zhang X, Zhao L. Utility of physiologically based pharmacokinetic absorption modeling to predict the impact of salt-to-base conversion on Prasugrel HCl product bioequivalence in the presence of proton pump inhibitors. AAPS J. 2017;19:1479–86.
141. Välitalo P, Ranta VP, Hooker AC, Kokki M, Kokki H. Population pharmacometrics in support of analgesics studies. Acta Anaesthesiol Scand. 2014;58:143–56.
142. Dubois A, Gsteiger S, Pigeolet E, Mentré F. Bioequivalence tests based on individual estimates using non-compartmental or model-based analyses: evaluation of estimates of sample means and type i error for different designs. Pharm Res. 2010;27:92–104.
143. Danchin A, Médigue C, Gascuel O, Soldano H, Hénaut A. From data banks to data bases. Res Microbiol. 1991;142:913–6.
144. Mohs RC, Greig NH. Drug discovery and development: role of basic biological research. Alzheimer's Dement Transl Res Clin Interv. 2017;3:651–7.
145. Lu J, Kong X, Liang Z, Luo C, Jiang H. Computational drug discovery. Acta Pharmacol Sin. 2012;33:1131–40.
146. Agoni C, Olotu FA, Ramharack P, Soliman ME. Druggability and drug-likeness concepts in drug design: are biomodelling and predictive tools having their say? J Mol Model. 2020;26.
147. Kubinyi H. Drug research: myths, hype and reality. Nat Rev Drug Discov. 2003;2:665–8.
148. Andrews CW, Bennett L, Yu LX. Predicting human oral bioavailability of a compound: development of a novel quantitative structure-bioavailability relationship. Pharm Res. 2000;17:639–44.
149. Yoshida F, Topliss JG. QSAR model for drug human oral bioavailability. J Med Chem. 2000;43:2575–85.
150. Pagliara A, Reist M, Geinoz S, Carrupt P-A, Testa B. Evaluation and prediction of drug permeation. J Pharm Pharmacol. 2010;51:1339–57.
151. Balimane PV & Chong S. Evaluation of permeability and P-glycoprotein interactions: industry outlook. in Biopharmaceutics Appl Drug Dev 101–138 (2008). https://doi.org/10.1007/978-0-387-72379-2_5.
152. Ikuo M. Development of fuzzy adaptive least-square and its uses in quantitative structure-activity relationship. Yakugaku Zasshi. 1995;115:805–22.
153. Johnson KC, Swindell AC. Guidance in the setting of drug particle size specifications to minimize variability in absorption. Pharm Res. 1996;13:1795–8.
154. Dressman JB, Amidon GL, Fleisher D. Absorption potential: estimating the fraction absorbed for orally administered compounds. J Pharm Sci. 1985;74:588–9.
155. Ding X, Rose JP, Van Gelder J. Developability assessment of clinical drug products with maximum absorbable doses. Int J Pharm. 2012;427:260–9.
156. Campbell, J. L., Clewell, R. A., Gentry, P. R., Andersen, M. E. & Clewell, H. J. Physiologically based pharmacokinetic/toxicokinetic modeling. Methods Mol Biol 929 (2012).
157. Brown RP, Delp MD, Lindstedt SL, Rhomberg LR, Beliles RP. Physiological parameter values for physiologically based pharmacokinetic models. Toxicol Ind Health. 1997;13:407–84.
158. Laomettachit T, Puri IK, Liangruksa M. A two-step model of TiO 2 nanoparticle toxicity in human liver tissue. Toxicol Appl Pharmacol. 2017;334:47–54.
159. Mukherjee D, Botelho D, Gow AJ, Zhang J, Georgopoulos PG. Computational multiscale toxicodynamic modeling of silver and carbon nanoparticle effects on mouse lung function. PLoS One. 2013;8:1–15.
160. Lin L, Wong H. Predicting oral drug absorption: mini review on physiologically-based pharmacokinetic models. Pharmaceutics. 2017;9:1–14.