Clin Pharmacokinet (2013) 52:415–431
DOI 10.1007/s40262-013-0042-0

REVIEW ARTICLE

Prediction of Drug Disposition on the Basis of its Chemical Structure

David Stepensky

Published online: 6 March 2013

Abstract The chemical structure of any drug determines its pharmacokinetics and pharmacodynamics. Detailed understanding of relationships between the drug chemical structure and individual disposition pathways (i.e., distribution and elimination) is required for efficient use of existing drugs and effective development of new drugs. Different approaches have been developed for this purpose, ranging from statistics-based quantitative structure–property (or structure–pharmacokinetic) relationships (QSPR) analysis to physiologically based pharmacokinetic (PBPK) models. This review critically analyzes currently available approaches for analysis and prediction of drug disposition on the basis of chemical structure. Models that can be used to predict different aspects of disposition are presented, including: (a) value of the individual pharmacokinetic parameter (e.g., clearance or volume of distribution), (b) efficiency of the specific disposition pathway (e.g., biliary drug excretion or cytochrome P450 3A4 metabolism), (c) accumulation in a specific organ or tissue (e.g., permeability of the placenta or accumulation in the brain), and (d) the whole-body disposition in the individual patients. Examples of presented pharmacological agents include "classical" low-molecular-weight compounds, biopharmaceuticals, and drugs encapsulated in specialized drug-delivery systems. The clinical efficiency of agents from all these groups can be suboptimal, because of inefficient permeability of the drug to the site of action and/or excessive accumulation in other organs and tissues. Therefore, robust and reliable approaches for chemical structure-based prediction of drug disposition are required to overcome these limitations. PBPK models are increasingly being used for prediction of drug disposition. These models can reflect the complex interplay of factors that determine drug disposition in a mechanistically correct fashion and can be combined with other approaches, for example QSPR-based prediction of drug permeability and metabolism, pharmacogenomic data and tools, pharmacokinetic–pharmacodynamic modeling approaches, etc. Moreover, the PBPK models enable detailed analysis of clinically relevant scenarios, for example the effect of the specific conditions on the time course of the analyzed drug in the individual organs and tissues, including the site of action. It is expected that further development of such combined approaches will increase their precision, enhance the effectiveness of drugs, and lead to individualized drug therapy for different patient populations (geriatric, pediatric, specific diseases, etc.).

D. Stepensky (✉)
Department of Clinical Biochemistry and Pharmacology, Faculty of Health Sciences, Ben-Gurion University of the Negev, POB 653, 84105 Beer-Sheva, Israel
e-mail: davidst@bgu.ac.il

1 Introduction

The effect of chemical structure on drug pharmacokinetics and on the resulting pharmacological effects has long been a topic of major interest, and has been based on empirical methods for studying structure–activity relationships. Starting from the first half of the twentieth century, significant developments have occurred in analytical chemistry, pharmacokinetics, pharmacodynamics, and other scientific fields, revealing the major mechanisms that determine drug activity [1, 2]. Detailed understanding of the processes of drug absorption and disposition (i.e., distribution and elimination) is required nowadays for effective development of new drugs and for more efficient use of existing ones. Therefore, several approaches for investigating these processes have been developed, reflecting

advances in the understanding of the pharmacokinetic behavior of drugs (Table 1). These approaches differ in many respects, including the chemical nature of the source data (diverse vs. homogeneous), the complexity of the model (the number of parameters), outcome (static or dynamic, e.g., the value of clearance vs. time course of drug concentration), prediction accuracy (absolute or relative deviation of predicted from observed data), etc.

Approaches to analysis and prediction of drug pharmacokinetics can be classified on the basis of the source and in-vivo reliability of the analyzed data. As shown in Table 1, methods for analysis of quantitative structure–activity relationships (QSAR) or quantitative structure–property or structure–pharmacokinetics relationships (QSPR), for example multiple linear-regression analysis or artificial neural networks (ANN), can be used to analyze the relationship between drug's chemical structure and the analyzed pharmacokinetic data without any mechanistic description of their connection. In-vitro experimental systems (cell-free, sub-cellular, or cell-based) can reflect certain mechanistic aspects that affect the value of a specific pharmacokinetic parameter. The physiological and/or mechanistic reliability of the model is maximum if ex-vivo or whole-body (in-vivo) models are used.

All of these approaches can be applied empirically or physiologically. For example, one or two-compartmental pharmacokinetic models can be used to describe drug disposition; however, these give limited insight into the mechanisms of drug disposition and their dependence on drug chemical structure. Physiologically based pharmacokinetic (PBPK) models that include numerous organs and tissues may provide more detailed and mechanistically based information about drug disposition behavior. However, such detailed PBPK models may not be required in some cases, because it has been shown that for many drugs the majority of the organs can be "lumped" together to 2 or 3 compartments with distinct shapes of drug concentration vs. time curves [3]. Indeed, "lumped" (or "hybrid" or "minimal") PBPK models can be successfully used to describe and predict the time course of drug concentrations in selected organs of interest [4, 5].

Table 1 Types of approach used to predict drug's pharmacokinetics

Type of approach	Examples of source data, in addition to the drug molecular descriptors (physicochemical properties)[a]
In-silico (QSPR)	Values of the individual pharmacokinetic data/processes (e.g., drug clearance or brain permeability)
Cell-free in-vitro systems	Drug retention on HPLC columns
	Drug interaction with artificial membranes
Sub-cellular in-vitro systems	Drug metabolism by liver microsomes
Cellular in-vitro systems	Drug permeation of cell monolayers
	Drug accumulation in red blood cells
Ex-vivo systems	Drug elimination by the perfused liver
In-vivo experiments	Organ/tissue weights, permeability coefficients, perfusion rates

HPLC high-performance liquid chromatography, *QSPR* quantitative structure–property (or structure–pharmacokinetics) relationships

[a] Interspecies scaling can be performed for most of these approaches on the basis of pre-clinical data (usually from mice, rats, or dogs) with or without allometric scaling factors [16, 17]

The physiological and/or mechanistic relevance of the specific prediction approach is important because of the complex interrelationships of the factors that determine drug pharmacokinetics (Fig. 1). The value of a pharmacokinetic parameter is determined by the drug's chemical structure (which can be described by use of molecular descriptors), physiological data, and, occasionally, also by the formulation/administration properties (level 0). Mechanistic physiologically based understanding of basic pharmacokinetic parameters (level 1) will lead to better prediction of the values of the higher-level parameters (levels 2 and 3) and the resulting time course of drug concentrations (level 4).

Models used to predict pharmacokinetics are seldom based directly on the chemical structure or molecular descriptors (Table 2) of the drug. Many models are based on indirect parameters derived from the drugs' chemical structure (e.g., drug solubility and/or permeability, or values of pharmacokinetic parameters that were measured in animal studies). For example, the rate-limiting step in oral drug absorption can be predicted on the basis of the water solubility and intestinal bioavailability (termed "permeability" by the US FDA) of the molecule, which serve the basis for the biopharmaceutics classification system (BCS) [6] that has been adopted by the FDA. These solubility and intestinal bioavailability parameters can either be measured (in in-vitro and in-vivo experimental settings, respectively) or predicted on the basis of the drug's chemical structure by use of one of the available software suites or QSPR models [7–9].

Historically, empirical methods, for example allometric scaling of clearance or volume of distribution parameters from in-vivo animal data, have been used extensively for prediction of drug disposition [10]. Recently, there has been a clear shift toward more extensive use of physiologically based models (PBPK; Fig. 2) [11–14], which are expected to reduce the uncertainty and increase the robustness of pharmacokinetic predictions [15–17].

The complexity of the models used to predict drug disposition is constantly increasing. Therefore, significant statistical, algorithmic, and computational challenges still remain to be overcome. Specifically, lack of standardization in the terminology that is used to report model precision (e.g., regression coefficient r^2, root mean square error

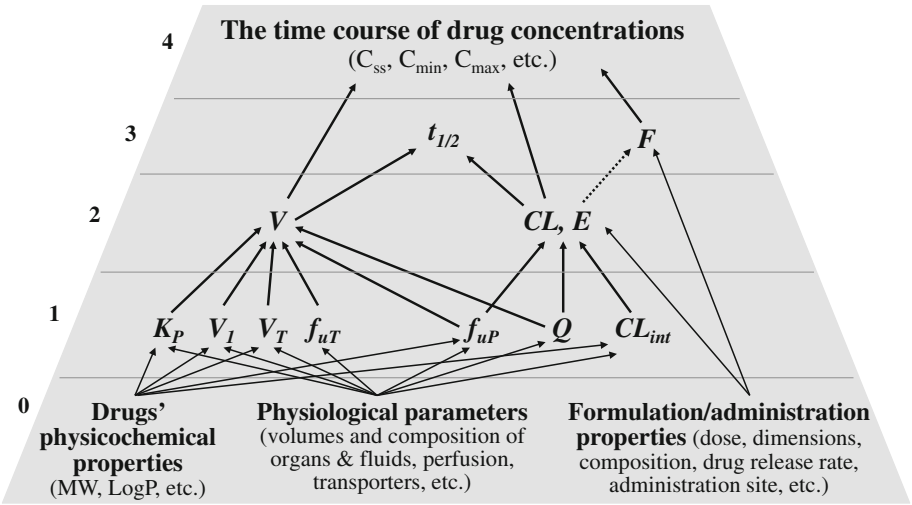

Fig. 1 The pyramid of factors that determine drug disposition (adapted from Mehvar [101]). Different levels of factors/parameters affect the pharmacokinetic behavior of the drug. Three groups of the underlying factors are the physicochemical properties of the drug, the physiological parameters of the body, and features related to drug administration (level 0). The interplay of these variables determines the values of the 1st level of pharmacokinetic parameters. For example, permeability coefficient (K_P) of drug accumulation in a specific tissue is determined by the drug size and/or lipophilicity and tissue composition and/or perfusion. Values of the volume of distribution and clearance (2nd level) reflect interplay of the underlying variables. For example, perfusion- or permeability-limited elimination of the drug by the liver depends on liver perfusion, the extent of binding to plasma proteins, and intrinsic clearance of the drug by the metabolic systems of the liver. Drug's volume of distribution and clearance govern its half-life, affect its input function after pre-systemic administration, and determine the time course of drug concentration (levels 3 and 4). The *dotted line* indicates pre-systemic first-pass metabolism of the drug, which can limit its systemic bioavailability (e.g., after oral administration). For simplicity, most of the variables which affect drug bioavailability are not shown. C_{max} maximum plasma drug concentration, C_{min} minimum plasma drug concentration, C_{ss} steady-state plasma drug concentration, CL the total body clearance of the drug, CL_{int} intrinsic clearance that reflects the expression levels and activity of the drug-metabolizing enzymes in the specific elimination organ and/or tissue, E extraction ratio of the drug from the blood and/or plasma in the specific elimination organ and/or tissue, F drug bioavailability, f_{uT} unbound fraction of the drug in the specific organ and/or tissue, f_{uP} unbound fraction of the drug in the plasma, K_P permeability coefficient, which reflects the affinity of a drug for a specific organ and/or tissue, Q perfusion in the individual organ and/or tissue, $t_{½}$ elimination half-life of the drug, V volume of drug distribution in the body, V_1 initial volume of drug distribution (usually, the volume of blood and/or plasma and the highly perfused tissues), V_T volume of the individual organ and/or tissue

Table 2 Examples of drug molecular descriptors that can be used to predict drug disposition

Molecular descriptors
Size (MW)
Shape
Molecular or polar surface area
log*P*
pK_a
Specific functional groups

logP partition coefficient, *pK*$_a$ acid dissociation constant, *MW* molecular weight

[RMSE], cross-validated correlation coefficient q^2, etc.) can obscure the differences between the individual approaches. Critical analysis and comparison of the major approaches on the basis of the precision of their predictions for a defined set of analyzed compounds can help overcome this problem [16–18].

In this review the major advances in prediction of drugs' disposition on the basis of their chemical structure are analyzed. The focus of the review is on pharmacological agents (and not on toxic compounds) and on prediction of their disposition (distribution and elimination, but not absorption) in human subjects (and not in animals, when data are available). This review does not describe in detail all the approaches available. Instead, the major direct and indirect approaches used to predict drugs' pharmacokinetics on the basis of their chemical structure are discussed, and recent advances and trends in this field are summarized. The contents of the review are organized according to the output of any specific approach: the values of individual pharmacokinetic parameters, the efficiency of the specific disposition pathway, accumulation in a specific organ or tissue, etc. (Table 3). In addition to analysis of low-molecular-weight (MW) compounds, recent advances in prediction of disposition of "non-classical" drugs are presented (biopharmaceuticals and drugs encapsulated in specialized drug-delivery systems [DDSs]).

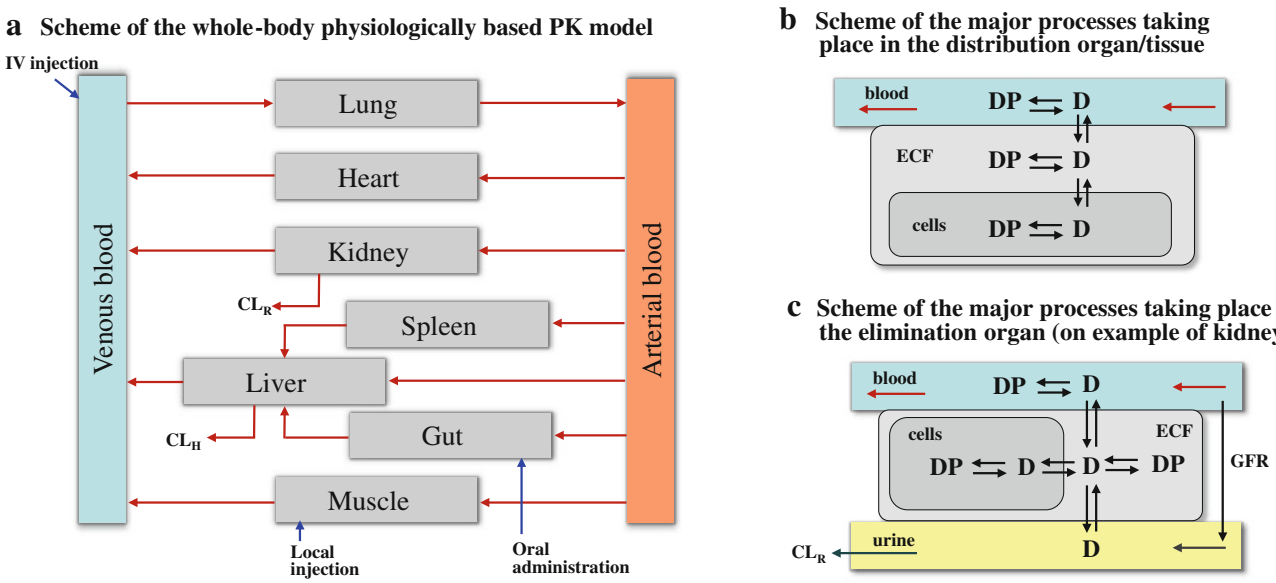

Fig. 2 The structure of the whole-body physiologically based pharmacokinetic (PBPK) model. **a** Schematic diagram of the whole-body PBPK model. For simplicity, only some of the body organs that are usually included in a model are shown. The characteristics of the individual organs include size (volume), perfusion (blood flow), and affinity for the drug (permeability coefficient). The organs can be classified according to their perfusion into low-perfused (usually fat, skin, and muscle) and highly perfused organs. The drug can be administered by several routes, undergoes distribution to the individual organs and tissues, and is eliminated by the liver (CL_H; hepatic clearance) and the kidneys (CL_R; renal clearance). **b** Schematic diagram of the major processes occurring in the individual distribution organ and/or tissue. The factors affecting the kinetics of the individual processes (*marked with arrows*) include the drug's physicochemical properties, affinity for proteins/lipids/phospholipids/other blood or tissue components, affinity for transporters, perfusion/convection, etc. As a result of these factors, accumulation of a drug in a specific organ/tissue can be perfusion- or permeability-limited. **c** Schematic diagram of the major processes occurring in the elimination organ (with kidney as an example). In addition to the factors presented in **b**, the drug undergoes urinary excretion and metabolism. For clarity, arrows representing drug metabolism and the fate of the metabolites formed are not shown. *D* drug, *DP* drug complex with proteins or other blood or tissue components (lipids, phospholipids, etc.), *ECF* extracellular fluid, *GFR* glomerular filtration rate

2 Prediction of Major Disposition Data for Low-Molecular-Weight Drugs

2.1 Volume of Distribution

Volume of drug distribution is a major pharmacokinetic parameter that relates total plasma (systemic) drug concentration to its amount in the body. The volume of drug distribution indicates the extent of drug extravasation from the systemic circulation and its relative accumulation in peripheral organs and tissues, which is determined by simple diffusion, facilitated diffusion, active (transporter-mediated) mechanisms, and binding to blood and tissue constituents (e.g., plasma protein binding), etc. Although the volume of drug distribution does not provide direct information about drug accumulation in the individual organs and tissues of the body, it is commonly used in drug discovery, development, and clinical practice as a measure of drug distribution [19]. In clinical settings, calculation of drugs' volume of distribution is not a routine task, because it requires intravenous dosing and measurement of drug concentrations in the systemic circulation. After extravascular dosing, volume of distribution can be determined

Table 3 Disposition data that can be predicted on the basis of drugs' physicochemical properties

Disposition data	Examples
Volume of distribution and individual distribution pathways	Steady-state volume of distribution
	Plasma–protein binding
	Permeability coefficients
	Accumulation in the red blood cells
Clearance: total body clearance and the individual disposition pathways	Total body clearance
	Hepatic clearance
	Biliary excretion
	Renal clearance
	Metabolism by specific enzymes (e.g. CYP3A)
	Transport by specific transporters (e.g. Pgp)
Distribution to the individual organs/tissues	Permeation via the blood–brain barrier
	Permeation via the placenta
	Accumulation in milk
Distribution within the specific organ/tissue	Intratumoral distribution of the drug and/or DDS

CYP cytochrome P450, *DDS* drug-delivery system, *Pgp* P-glycoprotein

from plasma drug concentration only if drug bioavailability is known. For this reason, many different approaches for prediction of volume of drug distribution in human subjects on the basis of pre-clinical experimental data have been developed. These approaches usually furnish values of steady-state volume of distribution (V_{ss}), a parameter that is frequently used in clinical pharmacokinetic calculations, e.g., of maintenance drug doses for an individual patient. It should be noted that the value of the apparent volume of distribution can increase or decrease as a result of drug redistribution between the plasma/blood and the extravascular fluids/tissues. For example, during multiple intravenous bolus administration of the drug, apparent volume of distribution fluctuates after each dose between the lower initial values (V_1, which are more appropriate than V_{ss} for calculation of loading doses), through V_{ss}, to the highest values (V_z, which reflect the pseudo-steady state between the central circulation and the extravascular fluids/tissues during the elimination phase). Gradual/prolonged drug absorption to the central circulation (e.g., in multiple oral dosing of drugs) can reduce or abolish these fluctuations and make V_{ss} values more relevant for calculation of drug doses.

Some of the approaches developed for prediction of human V_{ss} are based solely on the molecular descriptors of the drug. For example, QSPR approaches based on 2–4 molecular descriptors, such as partition coefficients, dipole moments, and the number of aromatic carbon atoms were developed for a dataset of 70 drugs [20]. The predictive power of this model was relatively high with the mean fold error of 2.01. In another study, 31 molecular descriptors and a dataset of 384 drugs were used for human V_{ss} prediction, and the geometric mean-fold error of the generated model was less than 2 [21]. Wajima et al. developed a hybrid approach based on a set of 64 drugs that combined partial least-squares analysis of 20 molecular descriptors and animal V_{ss} data [22]. The best of the developed models had $r^2 = 0.85$, and the V_{ss} value for 76.6 % of the drugs was predicted with less than twofold error.

Human V_{ss} can also be predicted on the basis of in-vitro drug binding to albumin and/or to artificial membranes. High-performance liquid chromatography-based measurement of human serum albumin binding and immobilized artificial membrane partitioning of 179 drugs revealed substantial correlation with human V_{ss} values ($r^2 = 0.76$) [23]. In another study, data reflecting in-vitro interaction of 121 analyzed compounds with the immobilized artificial membrane, their plasma protein binding and degree of ionization, and Øie–Tozer equation [19] were used to predict the human V_{ss} values ($r^2 = 0.82$; mean fold error less than 1.72) [24].

Most of the approaches used for prediction of V_{ss} are not based directly on the chemical structure or molecular descriptors of the analyzed drugs, but rather on collection and extrapolation of data obtained in vitro (in vitro–in vivo extrapolation, IVIVE) or from experimental animals. These approaches can be empirical in nature, with application of allometric scaling (without or with correction of inter-species differences in individual distribution factors, for example plasma protein binding of the drug). Alternatively, approaches based on the physiologically based parameters (tissue–plasma partitioning, tissue volumes, and blood flows) can be used. For example, approaches for prediction of human V_{ss} based on tissue-to-plasma partition coefficients (K_p) of muscle and fat [25], or muscle alone [26] have been developed. In-vitro experimental data in the form of unbound red blood cells partitioning, in combination with the tissue and/or plasma partition coefficients from animal studies and other supporting data, have been used by Poulin et al. [27] to predict the human V_{ss} of basic drugs.

Recently, several studies have attempted to classify and rank the performance of available methods for human V_{ss} prediction. Fagerholm [28] reviewed eight methods for prediction of human V_{ss}, including in-silico, allometric, and physiologically based models. The Pharmaceutical Research and Manufacturers of America (PhRMA) group launched an initiative on predictive models for human pharmacokinetics [29], and analyzed and compared 24 different methods for prediction of human V_{ss}. The authors classified these into empirical (allometric approaches without or with correction based on animal studies), semi-mechanistic (multicompartment PBPK models based on animal data with correction for inter-species differences in physiology), and mechanistic (whole-body PBPK) methods [16]. Lombardo et al. [30] analyzed and compared different approaches used to predict human V_{ss} on the basis of animal data.

Outcomes of these comparison studies indicate that current animal data-based approaches for human V_{ss} prediction are superior to in-silico (QSPR) or in-vitro (e.g., artificial membrane-based) methods. Apparently, the latter approaches can be successful for drugs that are distributed by passive diffusion but provide less accurate predictions for drugs with transporter and/or carrier-mediated distribution processes [28]. Thus, in-silico and in-vitro-based approaches can be recommended for use at the initial stage of drug development. Upon accumulation of in-vivo (preclinical and clinical) data, physiologically based allometric and PBPK approaches should preferably be used to predict the V_{ss} and individual disposition pathways of the investigated drug (i.e., its plasma protein binding, permeability coefficients in individual tissues, etc.) [16]. It should be noted that there is no single approach that performs best for all drugs, and the accuracy of the individual approach can be highly dependent on the structure of the molecule analyzed (e.g., acidic, basic, or neutral compound). The choice of the approach used for V_{ss} prediction should be based,

therefore, on available data and on the structural similarity of the drug to other compounds that have previously been analyzed (e.g., for a basic drug use methods that performed best for this group of compounds).

2.2 Clearance

Drug clearance (CL) is a major pharmacokinetic parameter that reflects the efficiency of elimination of the drug from the body. Several mechanisms can contribute to drug elimination, but low-MW drugs are usually assumed to be eliminated solely by the liver (via metabolism and biliary excretion) and kidneys (elimination in the urine, that can involve also renal metabolism). Efficiency of drug elimination is determined by the availability and intrinsic activity (CL_{int}) of specific metabolizing enzymes and the drug permeability (e.g., into the urine and metabolising organs), which depends on simple diffusion, facilitated diffusion, or active (transporter-mediated) mechanisms, and are affected by the drug binding to plasma proteins (f_u; Fig. 1). Different methods for prediction of drug clearance have been developed (reviewed elsewhere [10]). Similarly to prediction of V_{ss} (discussed in the section "Volume of Distribution"), most of these approaches are based not directly on drug structure, but rather on in-vitro or animal experimental data.

For prediction of the hepatic metabolic component of the drug elimination, several allometric scaling approaches have been proposed, with or without correction for interspecies differences in intrinsic clearance and drug plasma protein binding (CL_{int} and f_u, respectively). Alternatively, physiologically based IVIVE approaches can be used; these are based on in-vitro drug metabolism by microsomes, liver slices, or isolated or cultured hepatocytes (human or other species) [31, 32]. Fagerholm [33] reviewed five methods for prediction of human hepatic metabolic clearance and their modifications (correction using f_u and scaling factors) and concluded that physiologically based IVIVE approaches based on human or rat hepatocytes enabled accurate prediction (maximum ~twofold error; <25 % error for half of compounds) whereas the performance of allometric and microsome-based approaches (with or without modifications) was poor.

Several methods for prediction of renal clearance (CL_R) have been also proposed, including allometric and physiologically based IVIVE approaches; they are, however, generally characterized by poor performance (reviewed elsewhere [34]). This outcome stems from the multifactorial pathways of renal clearance that may include passive and active tubular transport mechanisms (in both directions, from the blood to the urine and vice versa), and cytochrome P450 (CYP) and uridine diphosphate-glucuronyltransferase (UGT)-mediated metabolism, etc. Under these conditions, methods that are based on molecular descriptors alone or on in-vitro data, can provide inaccurate predictions [10]. Improved predictions can be achieved by developing new physiologically based IVIVE methods that incorporate corrections for several factors, for example f_u, pH differences, and active transport mechanisms [34]. For example, Paine et al. [35] recently compared different approaches for prediction of human renal clearance on the basis of a dataset of 36 drugs and concluded that accurate predictions can be made on the basis of dog renal clearance data corrected for differences in plasma protein binding and kidney blood flow between dogs and humans ($r^2 = 0.84$, average fold error 2.2).

Instead of prediction of drug clearance from individual organs, total body clearance (i.e., the sum of the clearance from the liver, the kidneys, and other organs) can be analyzed by use of different approaches. The PhRMA group (discussed in the section "Volume of Distribution") compared 29 methods for prediction of total body clearance on the basis of 19 drugs with available clinical intravenous pharmacokinetic data (and 89 other drugs with available extravascular data) [17]. Several of these methods made use of drugs' molecular descriptors (MW, log*P*, etc.), in combination with other data. The authors reported that in-vivo methods performed slightly better than IVIVE methods for predicting human clearance (for the 19 analyzed drugs), and that the fold-error of the best-performing method was below 2 and 3 for 78 and 94 % of the compounds, respectively. In an even more recent publication, 37 methods for prediction of human clearance were compared on the basis of intravenous pharmacokinetic data from rat, dog, and monkey studies for approximately 400 compounds (the number of compounds analyzed for the individual methods ranged from 39 to 329, depending on data availability) [36]. The authors concluded that methods that used the monkey clearance values and a method correcting for differences in plasma protein binding between the rat and the human yield the best overall predictions (approximately 60 % compounds with geometric mean fold error ≤2).

From the studies summarized above, it seems that the hepatic clearance (CL_H) and CL_R values are most accurately predicted by use of physiologically based IVIVE approaches, and total body CL is best predicted by allometric scaling based on in-vivo monkey or rat data. The performance of models based solely on molecular predictors can be highly inaccurate for some classes of drug, e.g., for drugs that are eliminated via active transport processes in the liver and/or in the kidneys. It should be noted that there is a trend of increasing use of in-silico PBPK models for prediction of human clearance that are based on in-vitro experimental data [10]. These models can enable physiologically reliable integration of data from different sources, including the molecular

descriptors of the analyzed drugs and their metabolism by the individual CYP and UGT enzymes, and can lead to more accurate predictions of total drug clearance and of its components (CL_H and CL_R).

3 Prediction of Individual Disposition Pathways of Low-Molecular-Weight Drugs

3.1 Biliary Excretion

Biliary excretion is an important disposition pathway that is involved in elimination and enterohepatic cycling of some drugs. Biliary excretion occurs predominantly via adenosine triphosphate (ATP)-dependent efflux pumps, including organic anion transporters (OATPs), and its efficiency is highly dependent on the chemical structure of the drug (predominantly on the MW and lipophilicity) [37]. The effects of drug structure and biliary excretion have recently been analyzed by two research groups by use of an in-silico QSPR approach.

Yang et al. [102] developed equations based on molecular predictors (2D and 3D) to predict biliary clearance and the percentage of the dose excreted in the bile of rats and humans. It was found that the efficiency of biliary elimination depends on the charge of the molecule. MW threshold values for biliary excretion of organic anions of 400 and 475 g/mol were determined for rats and humans, respectively; cations or neutral compounds were not characterized by statistically significant MW threshold values. The values predicted by the QSPR model for biliary clearance in humans fell within the threefold error range of observed values, but the fraction of the dose excreted in the bile was predicted much less accurately.

Chen et al. [38] investigated the correlation of cumulative biliary excretion (measured in bile duct cannulated rats) and with 2D molecular descriptors of drug structure by use of a QSPR model. On the basis of analysis of 56 compounds with MWs in the 320–708 g/mol range, a quantitative equation that included seven molecular descriptors was developed and validated. The authors concluded that molecular hydrophobicity is the most important molecular property affecting cumulative biliary excretion (higher lipophilicity was associated with lower biliary excretion) with additional effects of the polarity and size of a molecule. The prediction performance of the developed model fell within threefold error range of observed cumulative biliary excretion for 74 and 60 % of the analyzed compounds for the training and validation sets, respectively, and within a fivefold error range for 85 % of the compounds (for both sets).

3.2 P-Glycoprotein Inhibition

P-glycoprotein (Pgp) is an energy-dependent efflux pump that has important effects on the bioavailability and disposition of many drugs. Pgp-dependent transport of a specific substrate molecule limits its oral bioavailability, reduces the extent of its body disposition (including its permeability to the brain, disposition via the placenta, etc.) and enhances its hepatic and renal excretion. Therefore, inhibition of Pgp can have a profound effect on drug pharmacokinetics. Chen et al. [39] analyzed the correlation between physicochemical properties of 1,273 molecules and Pgp inhibition (data from previous in-vitro measurements of Pgp inhibition) by use of recursive partitioning (RP) techniques and Bayesian categorization modeling. On the basis of molecular solubility, log *D* (the apparent partition coefficient at pH 7.4), MW, and other molecular properties, the authors were able to classify correctly the compounds into inhibitors (more than fivefold inhibition of Pgp-mediated transport) and non-inhibitors classes (less than fourfold inhibition of Pgp-mediated transport). Prediction accuracy was 81.7 % for the 973 compounds in the training set and 81.2 % for the 300 compounds in the test set. However, the applied approach was suitable for classification purposes only, and not for quantitative analysis of the extent of Pgp inhibition (e.g., concentration producing 50 % inhibition, IC_{50}, values). A similar limitation applies also to other previously developed approaches used to predict Pgp inhibition (summarized in Chen et al. [39]).

3.3 Cytochrome P450 3A Metabolism

CYP3A is the most abundant CYP in the human intestine and liver that contributes to the metabolism of drugs and limits their oral bioavailability (for example cyclosporine, nifedipine, verapamil, etc.). Thus, prediction of CYP3A-mediated metabolism can aid in prediction of drug elimination and bioavailability. Heikkinen et al. [40] investigated the intestinal metabolism of 20 CYP3A substrates by use of the GastroPlus® PBPK model. The authors compared predictions that were based on two types of intestinal permeability data. The "in-silico" approach (based on the combination of molecular predictors with in situ-rat wall permeability measurements) tended to underestimate intestinal metabolism with 20 and 65 % of the compounds falling into the 2- to 5- and 5- to 10-fold error range, respectively. On the other hand, intestinal permeability of 95 % of the analyzed compounds fell into the twofold error range for the "in-vitro" approach (based on permeability coefficients obtained in Madin Darby

canine kidney (MDCK) cell culture). By using the developed PBPK model, the authors were able to predict the plasma concentration time-course of the studied compounds and to perform detailed sensitivity analysis of the factors that affect their intestinal metabolism (e.g., drug solubility and dissolution).

3.4 Pharmacokinetic Interactions

Pharmacokinetic models can be used to predict drug–drug interactions (DDIs) and, thus, the required adjustments of drug dosing. Specifically, the effect of individual transport/elimination pathways on the time course of drug concentrations in the presence of other drugs can be predicted. Currently, prediction of DDIs is usually based on the outcomes of in-vitro measurements. For example, induction of CYP3A4 in clinical settings and its contribution to human clinical DDIs has been predicted on the basis of in-vitro measurements of CYP3A4 induction in hepatocyte cell culture, plasma and hepatocyte drug binding, and other parameters [41]. Similarly, in-vitro models based on suspended hepatocytes, liver microsomes, and sandwich-cultured hepatocytes have been used to determine the intrinsic clearance for 13 compounds and to predict human hepatic clearance and metabolism and transporter-based DDIs [42]. Complex interactions that take place in different organs and tissues can be analyzed by use of these tools [43, 44], taking into account metabolism and transporter effects, and permeability [45].

In summary, it can be stated that currently existing methods for prediction of individual disposition pathways of low-MW drugs are characterized by low accuracy. Some of these methods are suitable for classification purposes only, and can only partially suit the needs of the researchers in drug discovery and development. Most probably, improved methods for prediction of individual disposition pathways will come from the field of PBPK modeling. These models have been increasingly used during drug development and regulatory review in predicting the efficiency of the individual disposition pathways and their changes as a result of DDIs [46]. It should be noted that several currently available PBPK software packages, for example GastroPlus® and Simcyp Simulator®, incorporate molecular predictors for data input, can be used for assessment of the individual pharmacokinetic processes, and are suitable for prediction of the concentration time-courses of the studied drugs and their changes because of DDIs. It is expected that accumulating experimental data on the mechanisms and efficiencies of individual disposition pathways will be continuously incorporated into these models and will increase their precision and robustness.

4 Prediction of the Distribution of Low-Molecular-Weight Drugs to Individual Organs and Tissues

4.1 Blood–Brain Barrier Drug Penetration

Reliable estimation of drug permeation via the blood–brain barrier (BBB) is important for design of drugs acting on the CNS, and for safety assessment of drugs acting elsewhere in the body. The BBB is a complex structure and its permeation depends on the drugs' physicochemical properties, and on transport by means of influx and efflux pumps, including Pgp, breast cancer resistance protein (BCRP), OATP, amino acid transport systems, and others. Several QSPR models have been proposed for analysis of drug permeation via the BBB and brain accumulation based on molecular descriptors (summarized in Refs. [47, 48]); these differ in their structures, the data analyzed (e.g., brain-to-plasma ratios, cumulative brain accumulation, etc.), and predictive capabilities.

A QSPR model of passive transport via the BBB based on data from 178 drugs was recently proposed [47]. The analysis was based on kinetic drug permeation via the BBB (as the product of brain permeability and surface area, $\log P \times S$) in rats and mice, and did not take into account plasma protein binding and carrier-mediated effects. The model predicted experimental data correctly ($r^2 \sim 0.83$, RMSE <0.5) and indicated that BBB permeability depended on the drugs' octanol/water log*P* (in a bilinear fashion) and acid dissociation constant (pK_a) values. This approach was subsequently extended by the authors to incorporate the effect of drug binding to the brain and plasma constituents and to predict the brain accumulation of the studied drugs (as the steady-state brain/blood distribution ratio) [48]. The model was applied to a set of 470 compounds and included the descriptors: octanol/water log*P* of neutral species, ion fractions at pH 7.4, and the extent of drug plasma protein binding. The outcomes of the model were characterized by a good predictive power (RMSE = 0.4) and were indicative of a nonlinear, ionization-specific relationship between the above-listed descriptors and brain drug accumulation.

Shayanfar et al. [49] developed QSPR models to predict blood-to-brain concentration ratios separately for ionizable and un-ionizable compounds. The significant predictors for the un-ionizable compounds were $\log D_{7.4}$ (the octanol/water distribution coefficient at pH 7.4) and the MW. The predictors for the ionizable compounds were $\log D_{7.4}$ and the number of hydrogen bond acceptors. The developed models were validated and their prediction capabilities were within the twofold range for ~60 % of the compounds analyzed.

Improved prediction of drugs' BBB permeability and brain accumulation can be achieved by combination of

QSPR models with The Biopharmaceutics Drug Disposition Classification System (BDDCS) [50]. The BDDCS classifies the drugs according to the extent of their metabolism and solubility, and is an extension of the BCS system (discussed in the Introduction). In a recently published study, BDDCS class membership was integrated with in-vitro Pgp efflux and in-silico permeability data to categorize 153 drugs into BBB-permeable and impermeable classes (on the basis of available human and animal brain/plasma ratio data) [51]. This prediction was successful for more than 90 % of the drugs. Lower prediction success rate was obtained with a model based solely on molecular descriptors to predict the brain-to-plasma ratios of drugs and other chemical compounds in mice [52]. The authors used partial least-squares (PLS) analysis to identify five molecular descriptors that enabled correct classification of the analyzed compounds to low and high CNS exposure drugs (with brain-to-plasma ratios below or above 0.3, respectively) in ~75 % of cases [52].

Despite these achievements of QSPR models based directly on drugs' molecular descriptors, drugs' BBB permeability and brain accumulation in humans are most frequently predicted on the basis of the outcomes of in-vitro experimental data. Many different types of such approaches have been developed, by applying artificial membrane permeability assays (PAMPA), static and dynamic models based on brain microcapillary endothelial cells (BMEC), or based on other types of cell originating from different species (reviewed elsewhere [53]). Currently, these models reproduce the physiological behavior of the BBB better than in-silico models, and reflect more reliably the contribution of active transport systems and metabolic transformation to BBB drug permeability and disposition. It is expected that integration of in-silico, in-vitro, and PBPK models will enable better prediction of drugs permeation across the BBB and brain accumulation. Several recently published PBPK models of drug brain disposition [5, 54] are suitable for this purpose. Such integration is expected to provide a better understanding of drug-transport mechanisms and prediction of the kinetics of the processes studied (i.e., the time course of drug and metabolite concentrations in the brain, including differences in exposure of different brain regions to the drug [55]).

4.2 Permeability of the Placenta to Drugs

Despite the clear need for accurate fetal and neonatal health risk assessment, few methods exist for prediction of placental permeability on the basis of drugs' chemical structures. The ex-vivo human placental perfusion method is the most popular and reliable method for assessing placental transfer and metabolism [56] (usually measured as the placental clearance index or transfer index), despite being technically complex, time-consuming, and dependent on the availability of placentae from suitable donors. Several in-vitro models have been developed for analysis of the permeability to drugs of the placenta, including primary trophoblastic cells, immortal cell lines of placental origin, placental explants, and others, but they only partially reflect the active transport (influx and efflux transporter-mediated), metabolism, and tissue-binding mechanisms that occur in vivo [57].

Several QSPR models have been developed for analysis of the dependence of the placental transfer (measured by use of the ex-vivo human placental perfusion method) on the drugs' chemical structure, and critical analysis of several such models has been performed [58]. The accuracy of the five models analyzed ranged from poor to good (r^2 values from 0.63 to 0.86) and reflected the heterogeneity of the data set (from high to low, respectively). On the basis of analysis of these models, the authors concluded that hydrogen bonding and hydrophobicity were the major molecular descriptors that determine the transfer of drugs across the blood–placenta barrier. In addition, QSPR models can provide inaccurate prediction of the permeability of the placenta to drugs that undergo active transport or metabolism in the placenta.

Giaginis et al. [59] used a QSPR model to analyze placental permeability on the basis of a set of 84 compounds. The authors applied multivariate data analysis and generated a model based on 16 molecular descriptors that enabled good prediction ($r^2 = 0.73$, $q^2 = 0.71$, RMSE = 0.15) of relative placental permeability data (measured as placental clearance index normalized to data for antipyrine, a reference compound that undergoes passive diffusion only). According to this model, higher placental permeability was associated with the molecular properties (in order of their influence from highest to lowest) lower polarity, higher hydrophobicity, and larger molecular size. Generally, currently available QSPR models seem to be useful for prediction of placental permeability to drugs at the early stages of drug design [59], but confirmation of these predictions by use of ex-vivo human placental perfusion or animal studies is recommended at later stages of drug development.

4.3 Drug Accumulation in Mother's Milk

Even fewer data and approaches are available for prediction of the accumulation of drugs in mother's milk and its dependence on drugs' chemical structure. A simple model for prediction of milk/plasma (M/P) drug concentration ratios on the basis of pK_a, plasma protein binding, and octanol/water partition coefficients has been applied and had good prediction characteristics for a set of 10 basic drugs [60]. However, this model provided unreliable

predictions of *M*/*P* ratios for a set of 69 drugs with more diverse chemical properties (e.g., acidic, basic, and neutral compounds, etc.) [61]. Subsequently, Zhao et al. [62] developed an approach for prediction of *M*/*P* ratio classification (*M*/*P* ratio lower or higher than 0.1) based on a set of 126 drugs. The authors used a support vector machine analysis method that resulted in ~90 % classification accuracy and identification of the five major classifying molecular descriptors, the most important being the log*P* of the drug (higher log*P* values were associated with lower *M*/*P* ratios). Unfortunately, this model is suitable for classification purposes only and does not provide quantitative prediction of the *M*/*P* ratio values.

From the above discussion it can be seen that several approaches have been developed to predict the distribution of low-MW drugs to individual organs and tissues. Currently available approaches for prediction of the permeability of the BBB and placenta to drugs, and their accumulation in the mothers' milk are insufficiently accurate and do not satisfy the needs of researchers in drug discovery and development. It should be noted that there is a high structural resemblance of the processes that govern drug permeability via the BBB and placenta, for example expression of drug transporters (e.g., Pgp, BCRP, OATP, etc.) [63, 64], and their specific resemblance with the processes that determine drug accumulation in mother's milk. Therefore, drug permeation via all of these barriers can be eventually described by a single physiologically based model that will reflect the structural and functional characteristics of the above-mentioned barriers.

Prediction of drug permeability should not necessarily focus on a narrow subset of organs/tissues only. Use of unified algorithms to predict tissue-to-plasma partition coefficients can be developed on the basis of individual tissue composition data (abundance of proteins, lipids, charged phospholipids, etc.) and used for analysis of drug disposition [65–67]. Furthermore, the same data can be used to predict drug distribution at the subcellular level in the individual organs [68].

5 Prediction of the Disposition of Low-Molecular-Weight Drugs in Individual Patients and Special Populations

Inter and intra-subject variability in drug disposition is an additional challenge that should be overcome for efficient clinical application of prediction methods. To this end, parametric and nonparametric population-modeling approaches can be used [69]. The objective is to identify subpopulations of patients that differ in patterns of drug disposition and to identify covariates that are associated with these differences (e.g., age, sex, markers of hepatic and renal function, etc.). Currently, population-modeling approaches usually apply compartmental pharmacokinetic models (e.g., one or two-compartmental model) with a small number of disposition parameters to analyze in-vivo experimental data (from animal or clinical studies) [70, 71]. This may limit physiological/mechanistic insights into the processes of drug disposition that can be obtained from this analysis.

From the previous sections it is clear that a substantial amount of knowledge is available on the relationships between the structure and physicochemical properties of low-MW drugs, body physiology, and their combined effects on drug distribution in and elimination from individual organs and tissues. These data and relationships can be integrated into PBPK models and used in drug discovery, development, and regulation [11, 12]. Several proprietary modeling software products (for example Simcyp Simulator® and GastroPlus®) have been developed that can incorporate the model of drug dissolution, absorption, and metabolism in the gastrointestinal tract, the whole-body PBPK model, data on expression levels of metabolizing enzymes and transporters, etc. Users have limited control over the choice of structural properties and features of these models. Alternatively, more flexible but less user-friendly tools, for example general-purpose or biomathematical modeling software suites (MATLAB®, ADAPT 5, NONMEM, WinNonLin, etc.), can be used to generate custom-designed PBPK models [11].

All these tools can be used to analyze the effect of individual parameters (e.g., parameters related to the chemical structure of the drug) on drug disposition and to predict answers to many clinically relevant questions. For instance, drug disposition in geriatric or pediatric patients, in patients with compromised hepatic or renal function, in obese patients, in patients that have specific genotype (that dictates the activity of drug transporters and metabolic enzymes), or in other (patho)physiological conditions can be predicted on the basis of the drugs' chemical structure [11, 12]. An example of this approach is the in-silico prediction of disposition of three model drugs during pregnancy by use of Simcyp Simulator® PBPK model that integrates changes in the activity of three CYP enzymes [72]. This model was developed by applying a database of physiological, anatomical and metabolic changes that occur during normal pregnancy [73], and provided good predictions of changes in the plasma concentration vs. time curves of the analyzed drugs (that were within twofold of the observed values) [72].

On the basis of these PBPK models, the effects on drug disposition of individual variables incorporated into the model can easily be predicted. However, these predictions

should be interpreted with caution. For instance, compromised renal function leads to global changes in the drug metabolism and disposition, including tissue perfusion, liver metabolic activity, etc. [74]. These changes should be taken into account for reliable prediction of possible changes in drug disposition as a result of the acute or chronic kidney disease. Moreover, the drug's chemical structure is commonly incorporated into the PBPK models indirectly, in the form of solubility, permeability, affinity for transporters, rates of metabolism by the CYP enzymes, etc. Therefore, prediction of effect of alteration of the drug's chemical structure on its disposition (e.g., during drug discovery) requires correction of all the drug chemical structure-dependent parameters that determine the individual processes of distribution and elimination.

6 Prediction of the Disposition of Biopharmaceuticals and Drug-Delivery Systems

The previous sections of this review summarized the approaches used for prediction of disposition of low-MW compounds. In recent years, the number of therapeutics has expanded to include the biopharmaceuticals and drug-delivery systems (DDSs), which are characterized by different disposition patterns and require development of specialized prediction approaches that take into account their unique disposition features (Table 4). These approaches usually are not based directly on the physicochemical properties of the analyzed drug or DDS, but in some cases incorporate parameters that reflect the efficiencies of the individual disposition processes as a function of chemical structure (e.g., amino acid sequence for protein drugs), DDS composition, etc.

6.1 Disposition of Therapeutic Antibodies

In recent years, disposition of biopharmaceuticals and, specifically, of therapeutic antibodies has been a topic of extensive research. It is well known that the major processes of disposition of therapeutic antibodies are proteolysis (which can occur in any of the body tissues and fluids), uptake and partial degradation in the capillary endothelial cells (the process that is mediated by the neonatal Fc receptor, FcRn), and interaction with the target (the antigen) [75]. These disposition processes are very different from the fate of low-MW drugs (that are usually assumed to be eliminated by the liver and kidneys only), and some are non-linear (saturable) in the therapeutic range of concentrations. To describe the saturable interaction of the therapeutic agents with their targets, a target-mediated drug disposition (TMDD) model has been developed [76] and applied for quantitative analysis and prediction of the time course of the antibody's systemic concentrations [77, 78]. According to the TMDD model, the antibody undergoes disposition according to the 1- or 2-compartment pharmacokinetic model, with additional rate constants for antibody–target association and dissociation (that indirectly reflect the chemical structure of the F_V variable domains of the antibody). More detailed PBPK models that incorporate antibody binding to the FcRn (via the antibody's Fc region) in the individual organs and tissues have been developed recently and used to analyze and predict the time course of antibody disposition [79, 80]. Subsequently, a PBPK modeling approach incorporating a catenary sub-model of endosomal transport has been used to predict the relationship between the sequence of an antibody's Fc region and its affinity for the FcRn and its whole-body disposition [81]. Engineering of antibodies' Fc regions has attracted much attention in recent years because it enables control of the

Table 4 Major disposition pathways for different classes of drugs

"Classical" low-MW drugs	Therapeutic antibodies	Systemically administered DDS
• Binding to plasma proteins or other blood components (lipids, phospholipids, etc.)	• FcRn-dependent uptake and partial recycling by the vascular endothelium	• Release of the encapsulated drug
• Distribution into individual organs and tissues, binding to tissue components	• Distribution into individual organs and tissues	• Interaction with endogenous plasma components (formation of "corona")
• Hepatic metabolism	• Accumulation in the tumor or in the inflamed tissues (EPR effect)	• Degradation in the systemic circulation
• Biliary clearance	• Binding to the target	• Aggregation in the bloodstream
• Renal excretion	• Catabolism in the systemic circulation or at the distribution sites	• Uptake by mononuclear phagocyte system (MPS) cells
• Renal metabolism		• Uptake by the endothelial cells
		• Uptake by the red blood cells
		• Permeation to the target organ (e.g., the tumor) and local degradation
		• Permeation to other organs and tissues and local degradation

DDS drug-delivery systems, *EPR* enhanced permeability and retention, *FcRn* neonatal Fc receptor, *MW* molecular weight

antibodies' half-life and can be used to increase the efficiency of treatment with these agents.

6.2 Tumor-Targeted Delivery of Biopharmaceuticals

In contrast with TMDD models, whole-body PBPK models enable prediction of the time course of antibody concentrations in specific target organs and tumors. For example, accumulation of the CC49 antibody in the tumor and other tissues of tumor-implanted nude mice has been quantitatively analyzed by use of a specially developed PBPK model [80]. In addition to the parameters commonly used in these models (tissue volumes, perfusion, permeability coefficients), this model included parameters that reflect the factors that determine accumulation of the antibody in the tumor tissue (size of the antibody, osmotic coefficient, tumor antigen concentration, etc.). Thus, this model includes the major processes that can lead to enhanced permeability and retention (EPR effect) of antibodies and other macromolecules in the tumor tissues [82]. The model has also been used to predict the disposition of divalent and tetravalent single-chain variable region structures of CC49 in mice and the outcomes of this test were indicative of good applicability of the model [80].

Detailed modeling analysis of the effects of dose, molecular size, and binding affinity on accumulation of antibodies, their fragments, and other macromolecules by the tumor has been performed [83–85], revealing a complex interplay of these factors. Specifically, intermediate-sized targeting agents (MW ~25 kDa) were predicted to have the lowest tumor uptake, compared with agents of smaller and larger size. This analysis suggests smaller agents can accumulate rapidly in the tumor but require high affinity for the tumor antigens to be retained whereas retention of larger agents can be high even if their affinity for the tumor is low [84]. Unfortunately, efficient accumulation of the agent in the tumor does not necessarily lead to efficient exposure of the tumor cells to the drug [86, 87]. Specifically, low-MW drugs and biopharmaceuticals have limited therapeutic penetration depth in the tumor (i.e., the region where the cells are exposed to therapeutic drug concentrations), that can be as low as 1–2 mm [88]. Therefore, strategies to enhance drug accumulation in the tumor, and, specifically, permeation of the drug to the "deep" parts of the tumor (i.e., the cells that are distant from the blood vessels) are being developed, usually by applying specialized DDSs (discussed in the section "Tumor-Targeted Anti-Cancer Drug Delivery Using DDSs").

6.3 Tumor-Targeted Anti-Cancer Drug Delivery Using DDSs

In the past few decades significant progress has been made in the development of DDSs intended for targeted delivery of the drug to its site of action, e.g., in the tumor tissue. Encapsulation of the drug within the DDS masks its physicochemical properties and affects the pathways of its disposition in the body. Therefore, properties of both the drug and the DDS should be used for prediction of the disposition of the drug/DDS, and the resulting pharmacological activity. Quantitative analysis of the disposition of the drug/DDS, including tumor accumulation and, in some cases, intratumoral disposition of the drug/DDS also, has been performed in several studies.

For example, Thurber and Weissleder [89] used a systems approach to classify systemically administered drug/DDS into four categories depending on whether their uptake by tumors is limited by blood flow, extravasation, interstitial diffusion, or local binding and metabolism. PBPK models have been used to analyze the disposition of, and drug release from, long-circulating and temperature-sensitive liposomes loaded with a positron emission tomography probe [90], and to study the effects of size and charge on the disposition of composite (gold–dendrimer) nanoparticles [91].

Unfortunately, currently existing systemically administered DDSs accumulate to a small extent only in the tumor tissue, and more than 95 % of intravenously administered DDSs accumulate in other organs, in particular the liver, spleen, and lungs, and account for toxicity [92]. To increase drug concentrations in the tumor and limit extratumoral effects, anti-cancer drugs can be delivered directly into the tumor by use of focally (locally) administered DDSs. Disposition of the drug/DDS after focal intratumoral instillation of a drug-releasing implant has been analyzed in several studies. For instance, Arifin et al. [93] used a finite-element 3D model of the brain based on MRI reconstruction of brain geometry to analyze the role of convective transport in carmustine intratumoral disposition after Gliadel® implantation. The authors used the developed model to predict the effect of drug physicochemical properties on the efficiency of intratumoral disposition, and predicted that penetration of the drug into the tumor and buildup of efficient concentration were in the order paclitaxel > fluorouracil > carmustine > methotrexate [94]. However, even paclitaxel failed to penetrate some parts of the tumor tissue adequately. Fleming and Saltzman [95] analyzed the intratumoral distribution of carmustine eluted from Gliadel® implants and identified three pathways of drug transport. Drug penetration into the tumor was higher on the first day after implantation (5 mm) and declined on subsequent days, and simulations based on the developed models were consistent with these findings. In another study, simulations of intratumoral drug distribution indicated that paclitaxel released from the hydrogel OncoGel® and carmustine released from the Gliadel® wafers were characterized by similar therapeutic penetration depth

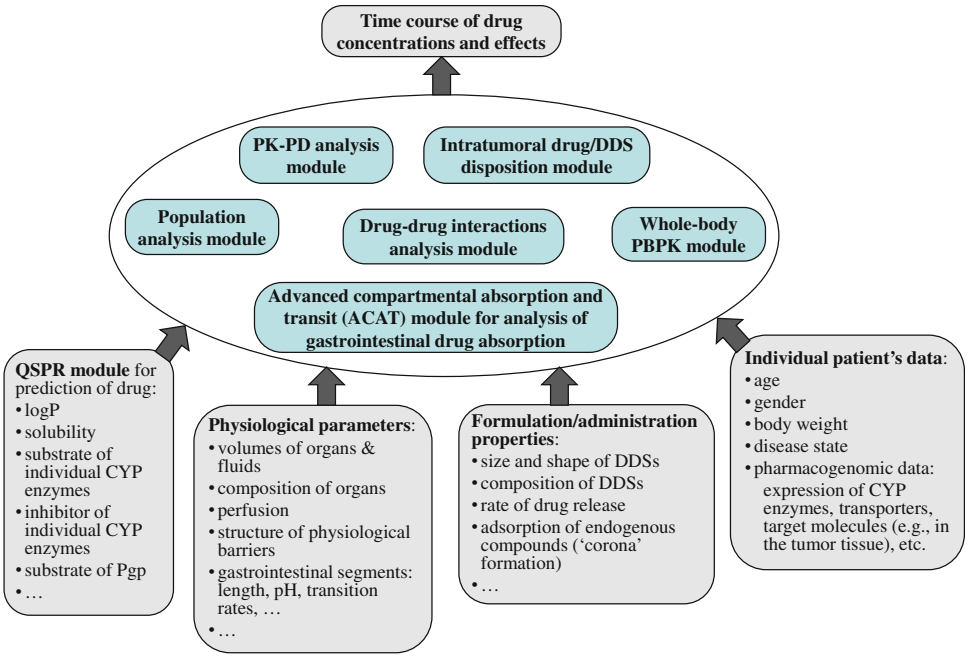

Fig. 3 Multi-component physiologically based model for analysis and prediction of the pharmacokinetics and pharmacodynamics of drug/DDS. *CYP* cytochrome P450, *DDS* drug-delivery system, *PBPK* physiologically based pharmacokinetic, *Pgp* P-glycoprotein, *PK-PD* pharmacokinetic and pharmacodynamic, *QSPR* quantitative structure-property (or structure-pharmacokinetic) relationships

(1–2 mm), but different duration of the effective therapeutic concentrations (30 vs. 4 days, respectively) [96].

These and other modeling-based studies provide important insight into the interactions of factors that determine the disposition of anti-tumor drug/DDSs and enable detailed analysis of intratumoral drug disposition, identification of rate-limiting factors in drug disposition, choice of drugs and design of DDSs with enhanced penetration and prolonged duration of effective therapeutic concentrations in the tumor tissue. It is expected that physiologically based models that incorporate parameters that reflect the chemical structure of the drug (for example molecular descriptors, or indirectly, such as affinity, stability, and permeability) and the composition and properties of the DDS will be increasingly used to analyze the disposition of drug/DDSs and to develop DDSs with higher intratumoral permeation and enhanced anti-cancer efficacy.

7 Conclusions

Several approaches for prediction of drug disposition have been developed that are based directly or indirectly on its chemical structure. These approaches differ in their physiological/mechanistic reliance, ranging from QSPR models that are based on statistical correlations to PBPK models that contain numerous physiological parameters in their structure. These differences in structure and complexity, and the availability of experimental data regarding the individual disposition processes, affect the principal characteristics of the available models: the chemical space of the analyzed compounds, model precision, robustness, ease/possibility of model validation, reliability of model extrapolations, etc. Different models, even if they analyze the same disposition process, cannot be easily compared because of the differences in the analyzed datasets and, sometimes, because different parameters are used to report prediction accuracy (discussed in the Introduction). Recently, several attempts have been made to compare the accuracy of existing methods (e.g., of V_{ss} or CL, discussed in the section "Prediction of Major Disposition Data for Low-Molecular-Weight Drugs") that can be helpful in choice of prediction method for a specific drug that is being investigated.

Most of the available methods focus on analysis of low-MW drugs and their fate, and tools that enable prediction of their disposition are generally available for such drugs, including:

1 the major pharmacokinetic parameters;
2 disposition pathways;
3 accumulation in the individual tissues; and
4 disposition changes in some pathological conditions.

Accurate prediction is usually defined as less than twofold difference between observed and predicted values [10]. On the basis of the studies analyzed in this review, the accuracy of current prediction approaches for low-MW drugs is insufficient and must be improved for more efficient application in drug discovery, development, and regulation. Despite the increasing clinical use of biopharmaceuticals and DDSs, their disposition is much less

studied than that of the low-MW drugs, and tools for analysis and prediction of their disposition are underdeveloped. Inefficient intratumoral permeability of biopharmaceuticals and DDSs are a major limitation of their clinical effectiveness in cancer treatment, and calls for the development of detailed mechanistically based approaches for analysis and prediction of the effect of formulation changes on the disposition of drug/DDSs. It is expected that this field will be the focus of extensive research in the next decade and that accumulating data on the individual pathways of disposition of DDSs will contribute to development of more precise and robust approaches for analysis and prediction of the fate of drug/DDS.

Despite their relative complexity, there is a trend for increased use of more detailed mechanistically based PBPK models. Such models allow detailed analysis of clinically relevant scenarios, for example the effect of the individual parameters on the time course of the analyzed drug in the individual organs and tissues [97–99], including the site of action. This trend reflects better understanding of the mechanisms that determine individual drug-disposition pathways, the possibility of deep and mechanistically based analysis of these data by use of the PBPK approach, and advances in the development of computers and software that make this analysis feasible. It is expected that the trend for increased use of PBPK models will continue, and that complexity of these models will tend to increase to reflect the complexity of the analyzed pathways and the accumulating experimental data on disposition of drugs and DDSs. It is plausible that whole-body PBPK models will be increasingly used in combination with other approaches, for example QSPR-based prediction of drug permeability and metabolism, pharmacogenomic data and tools, and pharmacokinetic–pharmacodynamic modeling approaches, etc. (Fig. 3).

Eventually, combinations of these tools will enable prediction of individualized drug therapy for patients from different populations (geriatric, pediatric, liver and kidney diseases, etc.), taking into account the efficiency of the individual disposition pathways and DDIs in the individual patient. Some of these tools are already available and can be used in combination with whole-body PBPK models, e.g., ADMET predictor [40] and ADME Prediction Toolbox [100]. Because of the limited accuracy of currently available prediction tools it seems they are best used iteratively when in-silico predictions are verified by use of more physiologically based tools (e.g., in-vitro, ex-vivo, or in-vivo measurements of the parameters studied), and the refined data are used in the next prediction–verification steps. It is expected that the accuracy of all the modules shown in Fig. 3 will continue to increase, that they will enable more reliable prediction of the disposition of drug/DDS on the basis of chemical structure, and they will contribute to more effective use of drugs in the future.

Acknowledgments No source of funding was used to prepare this review. The author has no conflicts of interest that are directly relevant to the content of this review.

References

1. Hochhaus G, Barrett JS, Derendorf H. Evolution of pharmacokinetics and pharmacokinetic/dynamic correlations during the 20th century. J Clin Pharmacol. 2000;40(9):908–17.
2. Atkinson AJ, Lalonde RL. Introduction of quantitative methods in pharmacology and clinical pharmacology: a historical overview. Clin Pharmacol Ther. 2007;82(1):3–6.
3. Pilari S, Huisinga W. Lumping of physiologically-based pharmacokinetic models and a mechanistic derivation of classical compartmental models. J Pharmacokinet Pharmacodyn. 2010; 37(4):365–405.
4. Cao Y, Jusko WJ. Applications of minimal physiologically-based pharmacokinetic models. J Pharmacokinet Pharmacodyn. 2012;39(6):711–23.
5. Liu X, Smith BJ, Chen C, et al. Use of a physiologically based pharmacokinetic model to study the time to reach brain equilibrium: an experimental analysis of the role of blood–brain barrier permeability, plasma protein binding, and brain tissue binding. J Pharmacol Exp Ther. 2005;313(3):1254–62.
6. Amidon GL, Lennernas H, Shah VP, et al. A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. Pharm Res. 1995;12(3):413–20.
7. Hou T, Wang J, Zhang W, et al. Recent advances in computational prediction of drug absorption and permeability in drug discovery. Curr Med Chem. 2006;13(22):2653–67.
8. Faller B, Ertl P. Computational approaches to determine drug solubility. Adv Drug Deliv Rev. 2007;59(7):533–45.
9. Jouyban A, Fakhree MAA, Shayanfar A. Solubility prediction methods for drug/drug like molecules. Recent Patents Chem Eng. 2008;1:220–31.
10. Lave T, Chapman K, Goldsmith P, et al. Human clearance prediction: shifting the paradigm. Expert Opin Drug Metab Toxicol. 2009;5(9):1039–48.
11. Rowland M, Peck C, Tucker G. Physiologically-based pharmacokinetics in drug development and regulatory science. Annu Rev Pharmacol Toxicol. 2011;51:45–73.
12. Rostami-Hodjegan A. Physiologically based pharmacokinetics joined with in vitro-in vivo extrapolation of ADME: a marriage under the arch of systems pharmacology. Clin Pharmacol Ther. 2012;92(1):50–61.
13. De Buck SS, Sinha VK, Fenu LA, et al. Prediction of human pharmacokinetics using physiologically based modeling: a retrospective analysis of 26 clinically tested drugs. Drug Metab Dispos. 2007;35(10):1766–80.
14. Jones HM, Gardner IB, Watson KJ. Modeling and PBPK simulation in drug discovery. AAPS J. 2009;11:155–66.
15. Jones HM, Parrott N, Jorga K, et al. A novel strategy for physiologically based predictions of human pharmacokinetics. Clin Pharmacokinet. 2006;45(5):511–42.
16. Jones RD, Jones HM, Rowland M, et al. PhRMA CPCDC initiative on predictive models of human pharmacokinetics, part 2: comparative assessment of prediction methods of human volume of distribution. J Pharm Sci. 2011;100(10):4074–89.

17. Ring BJ, Chien JY, Adkison KK, et al. PhRMA CPCDC initiative on predictive models of human pharmacokinetics, part 3: Comparative assessment of prediction methods of human clearance. J Pharm Sci. 2011;100:4090–110.
18. Wong H, Lewin-Koh SC, Theil FP, et al. Influence of the compound selection process on the performance of human clearance prediction methods. J Pharm Sci. 2012;101(2):509–15.
19. Stepensky D. The Øie–Tozer model of drug distribution and its suitability for drugs with different pharmacokinetic behavior. Expert Opin Drug Metab Toxicol. 2011;7(10):1233–43.
20. Ghafourian T, Barzegar-Jalali M, Hakimiha N, et al. Quantitative structure–pharmacokinetic relationship modelling: apparent volume of distribution. J Pharm Pharmacol. 2004; 56(3):339–50.
21. Lombardo F, Obach RS, Dicapua FM, et al. A hybrid mixture discriminant analysis-random forest computational model for the prediction of volume of distribution of drugs in human. J Med Chem. 2006;49(7):2262–7.
22. Wajima T, Fukumura K, Yano Y, et al. Prediction of human pharmacokinetics from animal data and molecular structural parameters using multivariate regression analysis: volume of distribution at steady state. J Pharm Pharmacol. 2003;55(7):939–49.
23. Hollosy F, Valko K, Hersey A, et al. Estimation of volume of distribution in humans from high throughput HPLC-based measurements of human serum albumin binding and immobilized artificial membrane partitioning. J Med Chem. 2006; 49(24):6958–71.
24. Sui X, Sun J, Li H, et al. Prediction of volume of distribution values in human using immobilized artificial membrane partitioning coefficients, the fraction of compound ionized and plasma protein binding data. Eur J Med Chem. 2009;44(11):4455–60.
25. Bjorkman S. Prediction of the volume of distribution of a drug: which tissue-plasma partition coefficients are needed? J Pharm Pharmacol. 2002;54(9):1237–45.
26. Rodgers T, Rowland M. Mechanistic approaches to volume of distribution predictions: understanding the processes. Pharm Res. 2007;24(5):918–33.
27. Poulin P, Ekins S, Theil FP. A hybrid approach to advancing quantitative prediction of tissue distribution of basic drugs in human. Toxicol Appl Pharmacol. 2011;250(2):194–212.
28. Fagerholm U. Prediction of human pharmacokinetics—evaluation of methods for prediction of volume of distribution. J Pharm Pharmacol. 2007;59(9):1181–90.
29. Poulin P, Jones HM, Jones RD, et al. PhRMA CPCDC initiative on predictive models of human pharmacokinetics, part 1: goals, properties of the PhRMA dataset, and comparison with literature datasets. J Pharm Sci. 2011;100(10):4050–73.
30. Lombardo F, Waters NJ, Argikar UA, et al. Comprehensive assessment of human pharmacokinetic prediction based on in vivo animal pharmacokinetic data, part 1: volume of distribution at steady state. J Clin Pharmacol. 2012. doi:10.1177/0091270012440281.
31. Poulin P, Hop CE, Ho Q, et al. Comparative assessment of in vitro-in vivo extrapolation methods used for predicting hepatic metabolic clearance of drugs. J Pharm Sci. 2012; 101(11):4308–26.
32. Poulin P, Kenny JR, Hop CE, et al. In vitro-in vivo extrapolation of clearance: modeling hepatic metabolic clearance of highly bound drugs and comparative assessment with existing calculation methods. J Pharm Sci. 2012;101(2):838–51.
33. Fagerholm U. Prediction of human pharmacokinetics—evaluation of methods for prediction of hepatic metabolic clearance. J Pharm Pharmacol. 2007;59(6):803–28.
34. Fagerholm U. Prediction of human pharmacokinetics—renal metabolic and excretion clearance. J Pharm Pharmacol. 2007; 59(11):1463–71.
35. Paine SW, Menochet K, Denton R, et al. Prediction of human renal clearance from preclinical species for a diverse set of drugs that exhibit both active secretion and net reabsorption. Drug Metab Dispos. 2011;39(6):1008–13.
36. Lombardo F, Waters NJ, Argikar UA, et al. Comprehensive assessment of human pharmacokinetic prediction based on in vivo animal pharmacokinetic data, part 2: clearance. J Clin Pharmacol. 2012. doi:10.1177/0091270012440282.
37. Hirom PC, Millburn P, Smith RL, et al. Species variations in the threshold molecular-weight factor for the biliary excretion of organic anions. Biochem J. 1972;129(5):1071–7.
38. Chen Y, Cameron K, Guzman-Perez A, et al. Structure–pharmacokinetic relationship of in vivo rat biliary excretion. Biopharm Drug Dispos. 2010;31(1):82–90.
39. Chen L, Li Y, Zhao Q, et al. ADME evaluation in drug discovery. 10. Predictions of P-glycoprotein inhibitors using recursive partitioning and naive Bayesian classification techniques. Mol Pharm. 2011;8(3):889–900.
40. Heikkinen AT, Baneyx G, Caruso A, et al. Application of PBPK modeling to predict human intestinal metabolism of CYP3A substrates—an evaluation and case study using GastroPlus. Eur J Pharm Sci. 2012;47(2):375–86.
41. Shou M, Hayashi M, Pan Y, et al. Modeling, prediction, and in vitro in vivo correlation of CYP3A4 induction. Drug Metab Dispos. 2008;36(11):2355–70.
42. Camenisch G, Umehara K. Predicting human hepatic clearance from in vitro drug metabolism and transport data: a scientific and pharmaceutical perspective for assessing drug–drug interactions. Biopharm Drug Dispos. 2012;33(4):179–94.
43. Fenneteau F, Poulin P, Nekka F. Physiologically based predictions of the impact of inhibition of intestinal and hepatic metabolism on human pharmacokinetics of CYP3A substrates. J Pharm Sci. 2010;99(1):486–514.
44. Rowland Yeo K, Jamei M, Yang J, et al. Physiologically based mechanistic modelling to predict complex drug–drug interactions involving simultaneous competitive and time-dependent enzyme inhibition by parent compound and its metabolite in both liver and gut—the effect of diltiazem on the time-course of exposure to triazolam. Eur J Pharm Sci. 2010;39(5):298–309.
45. Haddad S, Poulin P, Funk C. Extrapolating in vitro metabolic interactions to isolated perfused liver: predictions of metabolic interactions between *R*-bufuralol, bunitrolol, and debrisoquine. J Pharm Sci. 2010;99(10):4406–26.
46. Zhao P, Zhang L, Grillo JA, et al. Applications of physiologically based pharmacokinetic (PBPK) modeling and simulation during regulatory review. Clin Pharmacol Ther. 2011; 89(2):259–67.
47. Lanevskij K, Japertas P, Didziapetris R, et al. Ionization-specific prediction of blood–brain permeability. J Pharm Sci. 2009;98(1):122–34.
48. Lanevskij K, Dapkunas J, Juska L, et al. QSAR analysis of blood–brain distribution: the influence of plasma and brain tissue binding. J Pharm Sci. 2011;100(6):2147–60.
49. Shayanfar A, Soltani S, Jouyban A. Prediction of blood–brain distribution: effect of ionization. Biol Pharm Bull. 2011;34(2): 266–71.
50. Wu CY, Benet LZ. Predicting drug disposition via application of BCS: transport/absorption/ elimination interplay and development of a biopharmaceutics drug disposition classification system. Pharm Res. 2005;22(1):11–23.
51. Broccatelli F, Larregieu CA, Cruciani G, et al. Improving the prediction of the brain disposition for orally administered drugs using BDDCS. Adv Drug Deliv Rev. 2012;64(1):95–109.
52. Bergstrom CA, Charman SA, Nicolazzo JA. Computational prediction of CNS drug exposure based on a novel in vivo dataset. Pharm Res. 2012;29(11):3131–42.

53. Naik P, Cucullo L. In vitro blood–brain barrier models: current and perspective technologies. J Pharm Sci. 2011;101(4):1337–54.
54. Westerhout J, Ploeger B, Smeets J, et al. Physiologically based pharmacokinetic modeling to investigate regional brain distribution kinetics in rats. AAPS J. 2012;14(3):543–53.
55. Hammarlund-Udenaes M, Friden M, Syvanen S, et al. On the rate and extent of drug delivery to the brain. Pharm Res. 2008;25(8):1737–50.
56. Myren M, Mose T, Mathiesen L, et al. The human placenta—an alternative for studying foetal exposure. Toxicol In Vitro. 2007;21(7):1332–40.
57. Prouillac C, Lecoeur S. The role of the placenta in fetal exposure to xenobiotics: importance of membrane transporters and human models for transfer studies. Drug Metab Dispos. 2010;38(10): 1623–35.
58. Hewitt M, Madden JC, Rowe PH, et al. Structure-based modelling in reproductive toxicology: (Q)SARs for the placental barrier. SAR QSAR Environ Res. 2007;18(1–2):57–76.
59. Giaginis C, Zira A, Theocharis S, et al. Application of quantitative structure–activity relationships for modeling drug and chemical transport across the human placenta barrier: a multivariate data analysis approach. J Appl Toxicol. 2009;29(8):724–33.
60. Begg EJ, Atkinson HC, Duffull SB. Prospective evaluation of a model for the prediction of milk:plasma drug concentrations from physicochemical characteristics. Br J Clin Pharmacol. 1992;33(5):501–5.
61. Larsen LA, Ito S, Koren G. Prediction of milk/plasma concentration ratio of drugs. Ann Pharmacother. 2003;37(9):1299–306.
62. Zhao C, Zhang H, Zhang X, et al. Prediction of milk/plasma drug concentration (M/P) ratio using support vector machine (SVM) method. Pharm Res. 2006;23(1):41–8.
63. Vahakangas K, Myllynen P. Drug transporters in the human blood–placental barrier. Br J Pharmacol. 2009;158(3):665–78.
64. Giacomini KM, Huang SM, Tweedie DJ, et al. Membrane transporters in drug development. Nat Rev Drug Discov. 2010;9(3):215–36.
65. Peyret T, Poulin P, Krishnan K. A unified algorithm for predicting partition coefficients for PBPK modeling of drugs and environmental chemicals. Toxicol Appl Pharmacol. 2010; 249(3):197–207.
66. Graham H, Walker M, Jones O, et al. Comparison of in-vivo and in-silico methods used for prediction of tissue: plasma partition coefficients in rat. J Pharm Pharmacol. 2011;64(3):383–96.
67. Poulin P, Haddad S. Advancing prediction of tissue distribution and volume of distribution of highly lipophilic compounds from a simplified tissue-composition-based model as a mechanistic animal alternative method. J Pharm Sci. 2012;101(6):2250–61.
68. Poulin P, Haddad S. Microsome composition-based model as a mechanistic tool to predict nonspecific binding of drugs in liver microsomes. J Pharm Sci. 2011;100(10):4501–17.
69. Bustad A, Terziivanov D, Leary R, et al. Parametric and nonparametric population methods: their comparative performance in analysing a clinical dataset and two Monte Carlo simulation studies. Clin Pharmacokinet. 2006;45(4):365–83.
70. Duffull SB, Wright DF, Winter HR. Interpreting population pharmacokinetic-pharmacodynamic analyses—a clinical viewpoint. Br J Clin Pharmacol. 2010;71(6):807–14.
71. Kiang TK, Sherwin CM, Spigarelli MG, et al. Fundamentals of population pharmacokinetic modelling: modelling and software. Clin Pharmacokinet. 2012;51(8):515–25.
72. Gaohua L, Abduljalil K, Jamei M, et al. A pregnancy physiologically based pharmacokinetic (p-PBPK) model for disposition of drugs metabolized by CYP1A2, CYP2D6 and CYP3A4. Br J Clin Pharmacol. 2012;74(5):873–85.
73. Abduljalil K, Furness P, Johnson TN, et al. Anatomical, physiological and metabolic changes with gestational age during normal pregnancy: a database for parameters required in physiologically based pharmacokinetic modelling. Clin Pharmacokinet. 2012;51(6):365–96.
74. Verbeeck RK, Musuamba FT. Pharmacokinetics and dosage adjustment in patients with renal dysfunction. Eur J Clin Pharmacol. 2009;65(8):757–73.
75. Keizer RJ, Huitema AD, Schellens JH, et al. Clinical pharmacokinetics of therapeutic monoclonal antibodies. Clin Pharmacokinet. 2011;49(8):493–507.
76. Mager DE, Jusko WJ. General pharmacokinetic model for drugs exhibiting target-mediated drug disposition. J Pharmacokinet Pharmacodyn. 2001;28(6):507–32.
77. Wang W, Wang EQ, Balthasar JP. Monoclonal antibody pharmacokinetics and pharmacodynamics. Clin Pharmacol Ther. 2008;84(5):548–58.
78. Gibiansky L, Gibiansky E. Target-mediated drug disposition model: approximations, identifiability of model parameters and applications to the population pharmacokinetic-pharmacodynamic modeling of biologics. Expert Opin Drug Metab Toxicol. 2009;5(7):803–12.
79. Garg A, Balthasar JP. Physiologically-based pharmacokinetic (PBPK) model to predict IgG tissue kinetics in wild-type and FcRn-knockout mice. J Pharmacokinet Pharmacodyn. 2007; 34(5):687–709.
80. Davda JP, Jain M, Batra SK, et al. A physiologically based pharmacokinetic (PBPK) model to characterize and predict the disposition of monoclonal antibody CC49 and its single chain Fv constructs. Int Immunopharmacol. 2008;8(3):401–13.
81. Chen Y, Balthasar JP. Evaluation of a catenary PBPK model for predicting the in vivo disposition of mAbs engineered for high-affinity binding to FcRn. AAPS J. 2012;14(4):850–9.
82. Maeda H. Macromolecular therapeutics in cancer treatment: the EPR effect and beyond. J Control Release. 2012;164(2):138–44.
83. Thomas GD. Effect of dose, molecular size, and binding affinity on uptake of antibodies. Methods Mol Med. 2000;25:115–32.
84. Schmidt MM, Wittrup KD. A modeling analysis of the effects of molecular size and binding affinity on tumor targeting. Mol Cancer Ther. 2009;8(10):2861–71.
85. Wittrup KD, Thurber GM, Schmidt MM, et al. Practical theoretic guidance for the design of tumor-targeting agents. Methods Enzymol. 2012;503:255–68.
86. Minchinton AI, Tannock IF. Drug penetration in solid tumours. Nat Rev Cancer. 2006;6(8):583–92.
87. Florence AT. "Targeting" nanoparticles: the constraints of physical laws and physical barriers. J Control Release. 2012;164(2):115–24.
88. Ruenraroengsak P, Cook JM, Florence AT. Nanosystem drug targeting: facing up to complex realities. J Control Release. 2010;141(3):265–76.
89. Thurber GM, Weissleder R. A systems approach for tumor pharmacokinetics. PLoS One. 2011;6(9):e24696.
90. Qin S, Seo JW, Zhang H, et al. An imaging-driven model for liposomal stability and circulation. Mol Pharm. 2010;7(1): 12–21.
91. Mager DE, Mody V, Xu C, et al. Physiologically based pharmacokinetic model for composite nanodevices: effect of charge and size on in vivo disposition. Pharm Res. 2012;29(9):2534–42.
92. Bae YH, Park K. Targeted drug delivery to tumors: myths, reality and possibility. J Control Release. 2011;153(3):198–205.
93. Arifin DY, Lee KY, Wang CH, et al. Role of convective flow in carmustine delivery to a brain tumor. Pharm Res. 2009; 26(10):2289–302.
94. Arifin DY, Lee KY, Wang CH. Chemotherapeutic drug transport to brain tumor. J Control Release. 2009;137(3):203–10.
95. Fleming AB, Saltzman WM. Pharmacokinetics of the carmustine implant. Clin Pharmacokinet. 2002;41(6):403–19.

96. Torres AJ, Zhu C, Shuler ML, et al. Paclitaxel delivery to brain tumors from hydrogels: a computational study. Biotechnol Prog. 2011;27(5):1478–87.
97. Theil FP, Guentert TW, Haddad S, et al. Utility of physiologically based pharmacokinetic models to drug development and rational drug discovery candidate selection. Toxicol Lett. 2003;138(1–2):29–49.
98. Poulin P, Jones RD, Jones HM, et al. PHRMA CPCDC initiative on predictive models of human pharmacokinetics, part 5: prediction of plasma concentration-time profiles in human by using the physiologically-based pharmacokinetic modeling approach. J Pharm Sci. 2011;100(10):4127–57.
99. Vuppugalla R, Marathe P, He H, et al. PhRMA CPCDC initiative on predictive models of human pharmacokinetics, part 4: prediction of plasma concentration-time profiles in human from in vivo preclinical data by using the Wajima approach. J Pharm Sci. 2011;100(10):4111–26.
100. Jamei M, Marciniak S, Feng K, et al. The Simcyp population-based ADME simulator. Expert Opin Drug Metab Toxicol. 2009;5(2):211–23.
101. Mehvar R. Interdependency of pharmacokinetic parameters: a chicken-and-egg problem? Not! J Pharm Pharm Sci. 2006;9(1):113–8.
102. Yang X, Gandhi YA, Duignan DB, et al. Prediction of biliary excretion in rats and humans using molecular weight and quantitative structure–pharmacokinetic relationships. AAPS J. 2009;11(3):511–25.