Session 5: Drug Design By Molecular Modeling

Drug Discovery: Pharmacokinetic/Pharmacodynamic Fitting and Simulation

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Abstract

As widely known, more than 40% of the past failure in drug development is solely due to improper ADME properties of the new chemical entities (NCEs). The NCEs recognized exert highest pharmacological action may not be the optimize NCEs for further drug development. Based on convenience for the patients, the oral or any other extravascular dosage form such as nasal, pulmonary, rectal etc. are the most desired formulations. The extravasular dosing as a means for systemic treatment needs absorption process. Although the NCEs can exert significant pharmacological actions but have very low bioavailabiliy (BA), the pharmaceutical companies may discard these NCEs from their pipe lines. This leads to the concept of "Drug-Likeness" screening. However, the limitation in bioavailability can be the most important for the development of the oral formulations. Recently, the impact of absorptive/secretive processes on a drug's bioavailability has been recognized. Owe to the discovery of significantly vast numbers of the transporters on the surface of the cells which manage the uptake and efflux of NCEs and the possibility of integrate this knowledge with basic mathematical model for fitting the data or simulations, pharmaceutical companies can predict the biopharmaceutics and pharmacokinetics of NCEs more rapidly and precisely. The current available *in vitro* and *in vivo* techniques in combination with new in *silico* will significantly improve the drug discovery and development. Integration of the solid knowledge from chemical structure to pharmacokinetic until the final pharmacodynamics process which is the last objective for the benefits of the patients needs mechanistic approaches. These mechanistic approaches will be illustrated in this article in order to provide an overview and idea on what is available with regards to various experimental model.

Keywords: drug-likeness, pharmacokinetics, pharmacodynamics, Simulation, fittings, mathematical model.

The absorption process can occur in various route of administration. However, the principle of the absorption process via each route of administration is similar. Thus, the author would like to focus entirely on oral drug administration in this article. As widely known, more than 40% of the past failure in drug development is solely due to improper ADME properties of the new chemical entities (NCEs). The NCEs recognized exert highest pharmacological action may not be the optimize NCEs for further drug development. Thus, the focus of NCEs design is not solely on optimizing pharmacodynamic activity but also to ensure adequate pharmacokinetic properties (i.e.absorption, distribution, metabolism,and elimination) to enable suitable dosage forms/regimens to be developed. Oral drug administration is the most common and convenient route for chronic drug therapy [1]. Bioavailability is the term used to express both the extent and the rate at which unchanged drug proceeds from the site of administration to the site of measurement within the body. Oral bioavailability is directly related to the kinetic processes where by drug passes from the gastro intestinal tract (GIT) through the apical membrane of the epithelial cells

(i.e.enterocytes), through the enterocyte cells in to pre-hepatic blood vessels, which collect in the portal vein prior to passage through the liver, before reaching the systemic circulation. The bioavailability of the drug can be described as a fraction of dose escaping from GIT local instability (i.e. degradation, deactivation, insoluble etc.), intestinal mediated metabolism (so-called pre-hepatic first pass metabolism), and hepatic first pass metabolism. Numerous efforts exist to relate the use of physiochemical descriptors of drug molecules to the passive diffusion of drugs through biological membranes to predict the extent of absorption from the GIT. The pH partition hypothesis [2], physical model for passive diffusion [3], absorption potential [4], Lipinski's rule of five [5], quasi equilibrium model [6] and/or rule of unity [7] were used as tools for BA prediction. Although, many drugs have been recognized to penetrate the enterocytes via passive diffusion, recent studies have demonstrated that a number of drug transporters including uptake and efflux systems determine the membrane transport processes. Transporters are membrane proteins that are present in all organisms. These proteins control the influx of essential nutrients and ions and the efflux of cellular waste, environmental toxins, and other xenobiotics. The functions of membrane transporters may be facilitated (equilibrative, not requiring energy) or active (requiring energy). In considering the transport of drugs, pharmacologists generally focus on transporters from two major super-families, ABC (ATP binding cassette) and SLC (solute carrier) transporters. Most ABC proteins are generally active transporters and need ATP hydrolysis. There are 49 known genes for ABC proteins that can be grouped into seven subclasses or families (ABCA to ABCG) [8]. The most famous ABC transporters is P-glycoprotein (P-gp, encoded by ABCB1, also termed MDR1) which firstly discovered in resistant in cancer chemotherapy. The SLC superfamily includes genes that encode facilitated transporters and ion-coupled secondary active transporters that reside in various cell membranes. Transporters are very essential for all living cells. The numbers and types of transporters asymmetrically available in each side of the cell membrane are major contribution to the vectorial transport of any solutes resulted in efficient transfer of solutes across epithelial or endothelial barriers. For example, vectorial transport is important for hepato-biliary and urinary excretion of drugs from the blood to the lumen and in the intestinal absorption of drugs. Transporters work together with drug-metabolizing enzymes to eliminate drugs and their metabolites.

Due to the combination of passive diffusion, presystemic first pass metabolism; especially at the enterocytes and influx/efflux transporter generate the complexity of absorption process. The summary of these processes in enterocytes was illustrated in Figure 1.

Aforementioned above, although the absorption process seems to be complicated, it is not obstacle for a clever human species to understand and make use of combining all the knowledge together to generate the mathematical model in order to be able to fit the experimental results and to perform simulation for any specific scenarios of the interests to predict the outcomes. All the physicochemical, GIT physiological and dosage form/formulation factors as illustrated in Table 1 were included in the many absorption predictive model.

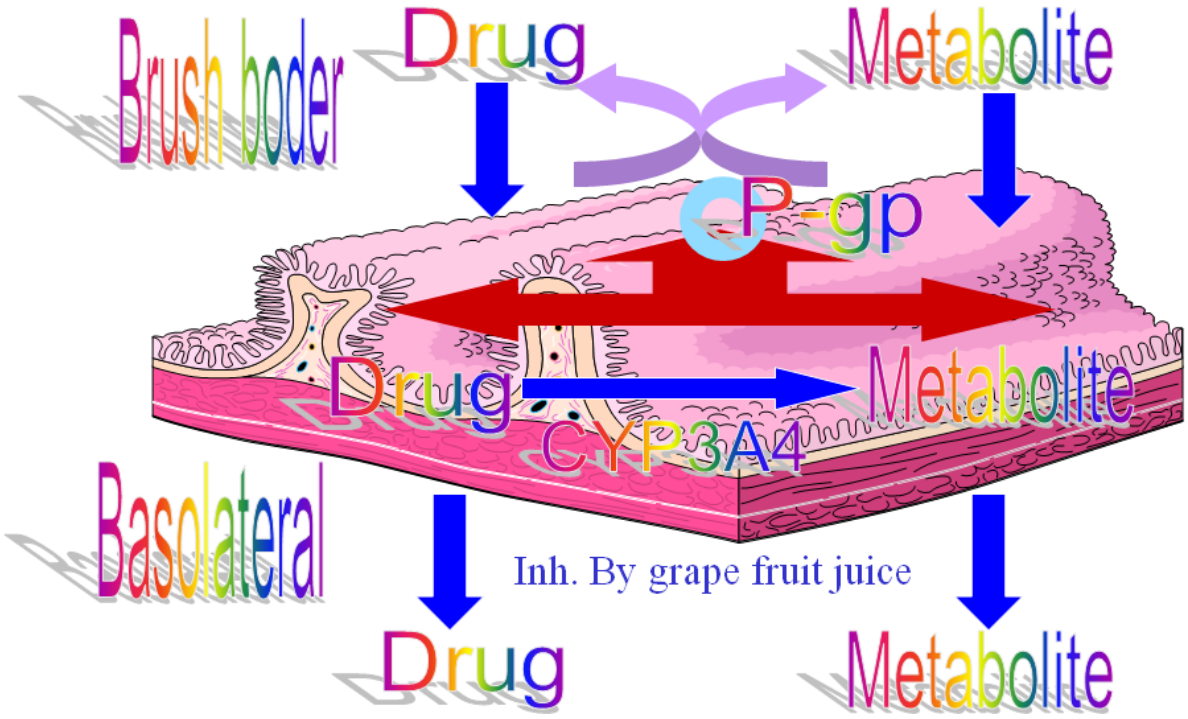


Figure 1: Complexity of absorption process. The P is parent drug and M is metabolite. P and M molecules can get in and out back and forth from the enterocytes before they can reach the systemic circulation.

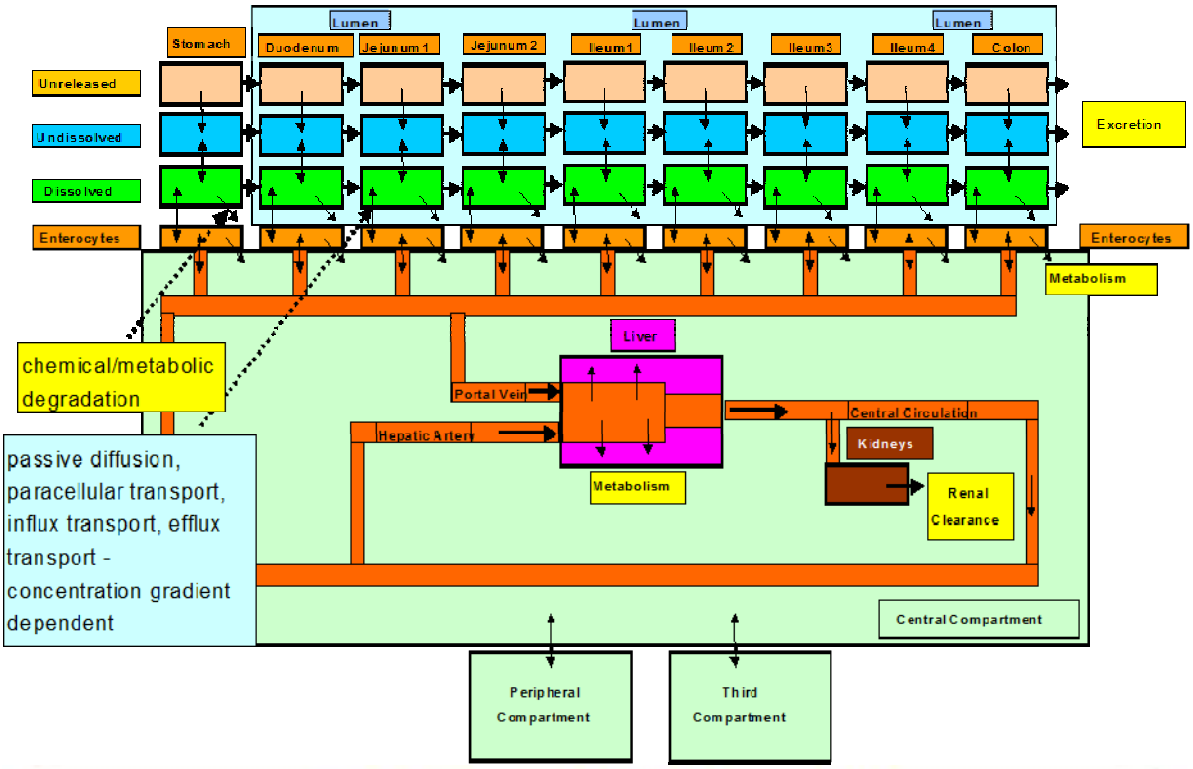
Physiochemical factors of drug substances	Physiological factors of GIT	Dosage form and formulation factors
Solubility	Stomach emptying rate	Dissolution rate
log *P*	Intestinal motility/flow rate	Disintegration rate
pK_a	Membrane surface area	Drug release mechanisms
H-bonding potential	Intestinal metabolism	Excipient effects
Molecular weight/size	Transport mechanisms	
PSA	Native surfactants	
	Intestinal secretions, e.g. mucous, enzymes	
	Intestinal blood/lymph flow	

GIT: gastrointestinal tract; PSA: polar surface area; log *P*: octanol/water partition coefficient.

Table 1 Factors influencing gastrointestinal absorption of drugs.

The mechanistic approaches with the system of equations with a few assumptions were developed to explain and predict BA of the NCEs. However, this approaches need an integration of the data obtained from *in vitro*, *in vivo* and/or in *silico*. Clearly, whole animal studies could not be used as a screening tool in a nearly development stage; therefore, *in vitro* models of intestinal absorption have been developed [9]. This in vitro system includes membrane-based (PAMPA: parallel artificial membrane permeation assay in high throughput fashion) [10], cell culture-based (including Caco-2 (Human colon adenocarcinoma cell, MDCK (Dog kidney epithelial cells) etc.) [11], and *ex vivo* models (Ussing chamber technique) [12, 13]. Each method has its pros and cons. The ability to accurately predict the oral absorption of drugs based solely on *in vitro* data provides an opportunity to assess the

developability, from an absorption point of view, of NCEs before any preclinical or clinical *in vivo* studies are performed. There have been several reports on physiologically based mathematical models that are capable of producing such predictions, and there area few commercially available software packages (e.g.,GastroPlus^{TM}, iDEA^{TM}, Intellipharm^{R} PK, Simp-cyp^{TM} and P K-SimR d etc.) that have been shown to predict the human absorption properties with a fairly high degree of accuracy. These software can support the pharmaceutical scientist to do the pharamcokinetics and/or pharmacodynamics prediction of NCEs in high throughput screening (HTS) fashion. All of the models used in the software are physiologically based. There are several different physiologically based approaches for the prediction of human oral absorption described in the literature. The models can be divided the different approaches into (1)qualitative methods such as the pH-partitioning hypothesis and the absorption potential (AP) concept and (2)quantitative methods including dispersion models, mass balance models, and compartmental absorption and transit models. The qualitative models aim to correlate physicochemical and physiological properties to the oral absorption of drugs in a simple way [14]. The example of the model used in Gastroplus TM using ACAT (Advanced Compartmental Absorption and Transit model) [15] and ADAM (Advanced Dissolution Absorption Metabolism) model [16] are illustrated below in Figure 2. As described earlier, absorption is a complex process that depends on several physiological and physicochemical properties. Thus these valuable models can facilitate the possibility of identification of potential risk for poor absorption based on a limited set of in vitro data in early drug discovery. The concept is used widely within the industry and is often used as a way to confirm that the physicochemical properties of a drug candidate are within an acceptable range [18]. Although several physiologically based mathematical models as mentioned above designed to predict absorption properties have been available and used for several years, good correlations have been shown between predicted and observed human BA for passively transported NCEs/compounds, slightly poorer correlations are normally obtained when drugs with significance levels of transport via transporter(s) [19]. Thus, the need to include the transporters data in the models is very valuable for the development of the more accurate prediction. Owe to the advance in cellular and molecular level study, the pharmacokinetics is moving to the concept of molecular pharmacokinetics. The roles of drug transporters can be assessed using in vitro and invivo, using techniques spanning from cellular expression systems to gene knock out animals. Research outcomes from such studies have been applied to clinical science and drug development. The studies of membrane vesicles and cultured epithelial cell lines have been used in the field since 1980s and this resulted in sustainable advancement in the field. At the end of 1980s, the molecular nature of drug transporters was unveiled by cDNA cloning and the first clinically important drug transporter, the P-glycoprotein(P-gp), was identified. The existence of further carriers, receptors and/or metabolic enzymes with overlapping substrate specificity complicates the generation and interpretation of suitable data.



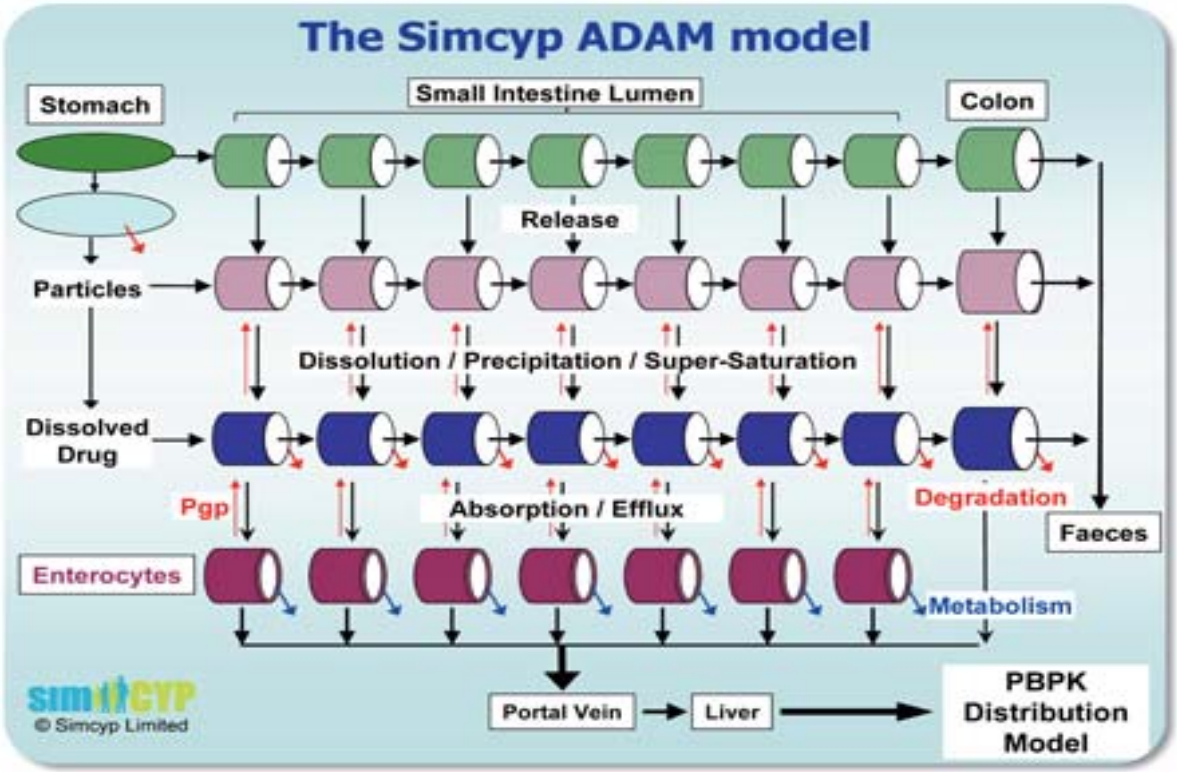


Figure 2 ACAT (Advanced Compartmental Absorption and Transit model) is illustrated in above figure and is illustrated in below figure.

The molecular expression cloning, polymerase chain reaction (PCR) cloning, and ***in silico*** homology screening strategies have been used in the field. It will be very crucial if isolation of transport proteins in sufficient amount and purity can be prepared as required for structural analysis. These data can be summarized and integrated in the mathematical model

for ***in silico*** prediction to improve the accuracy of the model for NCEs which are the substrate of any transporters.

Moreover, we should also consider the differences among the population in term of both inter-subject and intra-subject variability. The model can include a full physiologically-based pharmacokinetic (PBPK) model together with extensive libraries on demographics, developmental physiology and the ontogeny of drug elimination pathways using population pharmacokinetic approaches. Thus, as an example, it is possible to use the data from one age range such as adult to predict those from pediatric and geriatric. The example of the prediction of the clearance of caffeine from birth to adulthood is illustrated in Figure 3 [16].

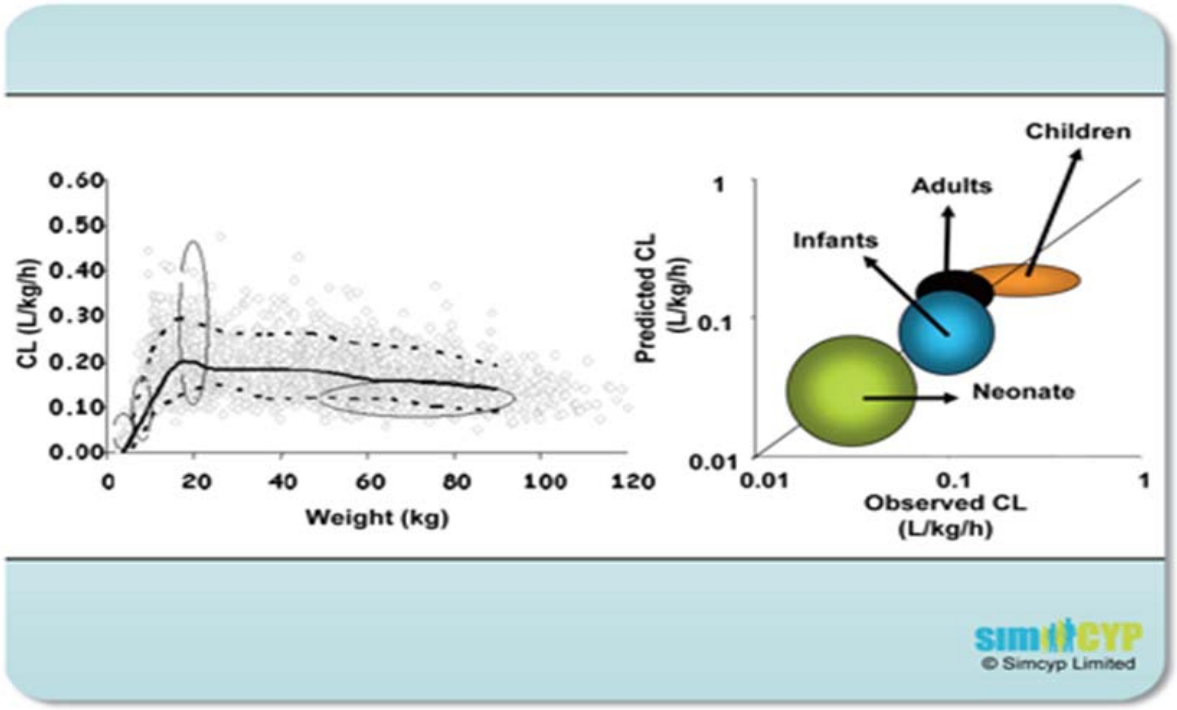


Figure 3 Prediction of the clearance of caffeine from birth to adulthood

In a few decades, it has long been identified that the genetic variability in metabolism process can interfere the pharmacokinetics of medicines and this variability can be observed differently in ethnic groups. There are the bimodal (poor/extensive metabolizers) or multimodal differences (poor/expensive/ultra metabolizers) in clearance among populations. This is recognized as "Genetic Polymorphism". In the midst of the discovery of transporters, it is not surprising that the genetic polymorphism of transport process can be elucidated. Thus, if we need to make more precise perdition, the genetic polymorphism information should be integrated. These aforementioned factors were integrated in few software such as Simcyp™. The population approaches whole body PBPK model with the ADAM™ model were used in this software as depicted in Figure 4.

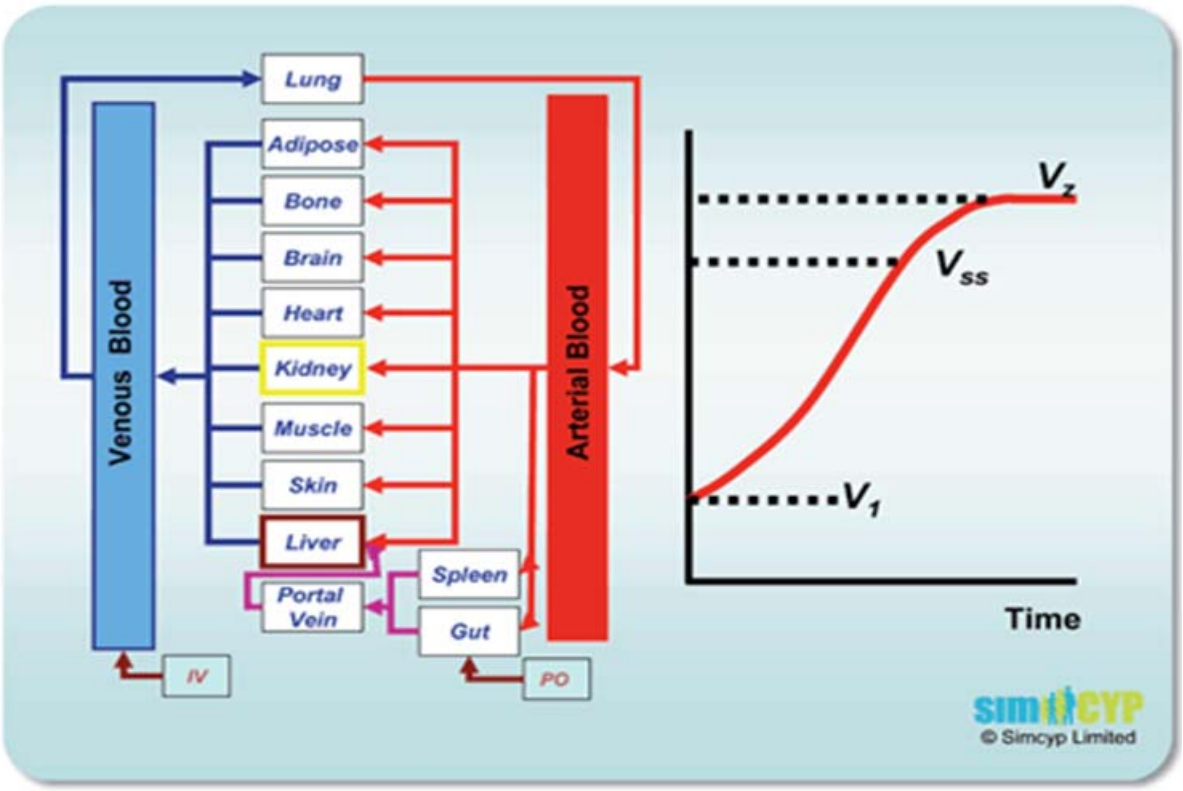


Figure 4 Whole body PBPK

In conclusion, the new era of the new drug discovery and development process is in progress. This new scheme of the process by integrating ***in vitro***, ***in vivo*** and ***in silico*** experiments into mathematical model for the NCEs screening can reduce the cost, attrition rate and time to get the new medicine in the market.

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