An Update on Pharmacokinetic Models

16

Ravi Shankar and Kamla Pathak

Abstract

The process and kinetics involved in drug distribution and disposition are complex, and drug events often happen simultaneously. The process is governed by a variety of factors that must be properly defined and quantified for designing optimum drug therapy regimens through pharmacokinetic models. A pharmacokinetic model is a hypothesis using mathematical terms to describe quantitative relationships and is efficient in describing the time course of the drug throughout the body and is helpful in computing and calculating desired pharmacokinetic parameters which are needed for achieving the overall objective of drug therapy. The predictive capability of a model lies in the proper selection and development of mathematical function(s) that parameterize the essential factors governing the kinetic process. Such mathematical models can be devised to simulate the rate processes of drug absorption, distribution and elimination to describe and predict drug concentrations in the body as a function of time. The field is under constant upgradation to match with recent and novel drug delivery systems and therapeutic approaches for achieving the overall objective of the therapeutic regimen.

Keywords

Conventional models · Pharmacokinetic models · Novel models

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16.1 Introduction

The movement of drugs inside the body is a very complex and continuous process starting from the blood to extracellular fluid to intracellular compartments and from this state to metabolism and finally excretion. The biological nature of drug distribution and disposition is complex, and drug events often happen simultaneously. The process is governed by a variety of factors, including the properties of drug molecules, blood flow rate and permeability across different membranes, and affinity between drugs and different tissue components. So, it is of utmost importance to consider these important factors when designing drug therapy regimens.

The process of designing an effective dosage regimen consists of determining the dose of the drug and time interval which directly depends upon the state and rate of different on-going processes.

A pharmacokinetic model is a hypothesis using mathematical terms to describe quantitative relationships and is efficient in describing the time course of the drug throughout the body and is helpful in computing and calculating desired pharmacokinetic parameters which are needed for achieving the overall objective of drug therapy. The predictive capability of a model lies in the proper selection and development of mathematical function(s) that parameterize the essential factors governing the kinetic process. A pharmacokinetic function relates an independent variable to a dependent variable, often through the use of parameters. Such mathematical models can be devised to simulate the rate processes of drug absorption, distribution and elimination to describe and predict drug concentrations in the body as a function of time (Jones and Rowland-Yeo 2013; Shargel et al. 2016). Pharmacokinetic models find their applications in:

1. Prediction of plasma, tissue and urine drug levels with any dosage regimen and relates it to the optimum therapeutic response or dosage regimen.
2. Calculation of the optimum dosage regimen for each patient individually called individualization of dosage regimen.
3. Estimation of the possible accumulation of drugs and/or metabolites.
4. Correlation of drug concentrations with pharmacologic or toxicology activity of the drug.
5. Evaluation of differences in the rate and extent of availability between formulations (bioequivalence).
6. Describing the effect of physiological alterations on the pharmacokinetic parameters finally relating it to pharmacodynamic parameters and the development of an effective therapeutic regimen. There should be insightful studies and caution should be there in ensuring that a suitable model would be chosen to fit the experimental data so that the correct pharmacokinetic parameter could be derived (Brahmankar and Jaiswal 2015).

16.2 Types of Pharmacokinetic Models

There are various well-established pharmacokinetic models (Fig. 16.1) that have been consistently used by academicians and researchers to understand the kinetic behaviour of drug molecules in the body. The subsequent text describes the traditional models used to elucidate the pharmacokinetic behaviour of drugs. These can be classified broadly as compartment models, non-compartment models and physiological models.

16.2.1 Compartment Models

Compartment modelling is the simplest and most commonly used model approach for the determination of pharmacokinetic parameters. This approach is based on the simple determination of plasma concentration with time data and its interpolation of the data to calculate various parameters. A compartment is not a real physiologic or anatomic region but is considered as tissue or group of tissues that have similar blood flow and drug affinity. Within each compartment, the drug is considered to be uniformly distributed. Mixing of the drug within a compartment is rapid and homogeneous and is considered to be 'well stirred', so that the drug concentration represents an average concentration, and each drug molecule has an equal probability of leaving the compartment. Rate constants are used to represent the overall rate processes of drug entry into and exit from the compartment. The model is an *open system* because the drug enters the system and also can be eliminated from the system simultaneously. Compartment models are based on linear assumptions using

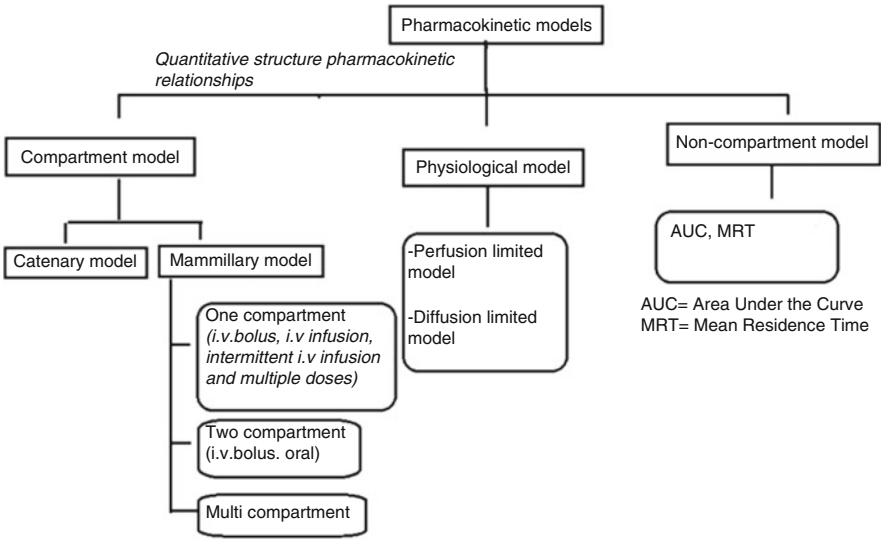


Fig. 16.1 Classification of conventional pharmacokinetic models

linear differential equations. Depending upon the arrangement of compartments, compartment modelling is further classified into (1) mammillary model and (2) catenary model (Notari 2013).

16.2.1.1 Mammillary Model

The mammillary model is the most common compartment model used in pharmacokinetics. The mammillary model is a strongly connected system because one can estimate the amount of drug in any compartment of the system after a drug is introduced into a given compartment. The central compartment is assigned to represent plasma and highly perfused tissues that rapidly equilibrate with a drug. When an intravenous dose of a drug is administered, the drug enters directly into the central compartment. Elimination of drugs occurs from the central compartment because the organs involved in drug elimination, primarily the kidney and liver, are well-perfused tissues.

In a two-compartment model, the drug can move between the central or plasma compartment to and from the tissue compartment. Although the tissue compartment does not represent a specific tissue, the mass balance accounts for the drug present in all the tissues. In this model, the total amount of drugs in the body is simply the sum of drugs present in the central compartment plus the drug present in the tissue compartment. The compartmental models are particularly useful when little information is known about the tissues.

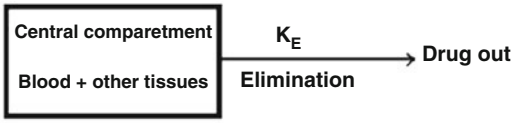
Several types of compartment models are described in Fig. 16.2. The pharmacokinetic rate constants are represented by the letter *k*. Compartment 1 represents the plasma or central compartment, and compartment 2 represents the tissue compartment. The drawing of models has three functions. The model (1) enables writing differential equations to describe drug concentration changes in each compartment, (2) gives a visual representation of the rate processes and (3) shows the pharmacokinetic constants that are necessary to describe the process adequately.

16.2.1.2 Catenary Model

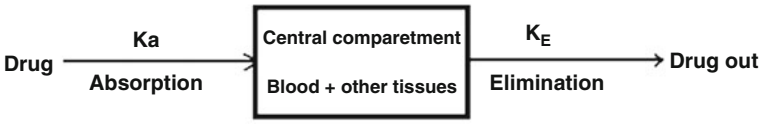
In pharmacokinetics, the mammillary model must be distinguished from another type of compartment model called the catenary model. The catenary model consists of compartments joined to one another like the compartments of a train (Fig. 16.3) in contrast to the mammillary model which consists of one or more compartments around a central compartment like satellites. Because the catenary model does not apply to the way most functional organs in the body are directly connected to the plasma, it is not used as often as the mammillary model.

The representation of drug distribution using mathematical compartment modelling has various limitations, which are partly pragmatic and partly the consequences of various assumptions we make about pharmacokinetics.

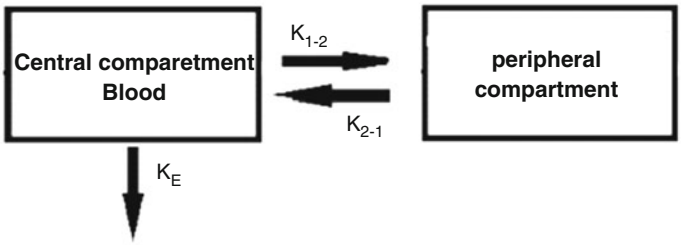
The common limitations associated with the compartment modelling approach are:



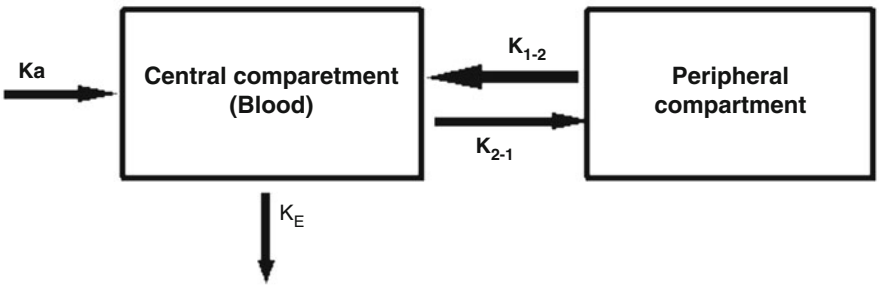
Model 1: One comparetment open model, intravenous administration



Model 2: One comparetment open model, extravascular administration



Model 3: Two comparetment open model, Intravenous administration



Model 4: Two comparetment open model, extravascular administration

Fig. 16.2 Types of compartment models

- The compartments and parameters are hypothetical and bear no relationship with actual anatomy and physiology that finally needs complex data interpretation for developing information,
- That the central compartment is the only compartment from which the drug is eliminated. In the case of cisatracurium where the drug degrades spontaneously

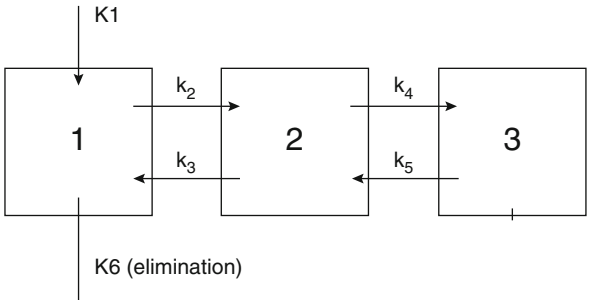


Fig. 16.3 Diagram for catenary model

no matter where it is in the body, i.e., elimination takes place in numerous compartments simultaneously.

- That the multicompartment model is more accurate the more compartments it has. This is not the fact and often the plasma concentration data derived from a two-compartment model matches the empiric data at least as well as the multicompartment prediction.
- The model utilizes complex multiexponential mathematical equations for determining pharmacokinetic parameters.
- The selection of models may vary with the drug, route of administration and study population.
- Interpretation and extrapolation of animal data to human data are quite a complex task (Notari 2013).

16.2.2 Physiological Model

The physiologically based pharmacokinetic model (PBPK) provides an exact description of the time course of drug concentration in any organ or tissue and is, therefore, able to provide greater insight into drug distribution in the body. Also, since the parameters of these models correspond to actual physiological and anatomical measures, such as organ blood flows and volumes, changes in the disposition kinetics of drug because of physiological or pathological alterations in body function may be predicted by perturbation of the appropriate parameter (s) (Aarons 2005). Finally, these models introduce the possibility of animal scale-up which would provide a rational basis for the correlation of drug data among animal species. A physiological pharmacokinetic model is composed of a series of lumped compartments (body regions) representing organs or tissue spaces whose drug concentrations are assumed to be uniform. The compartments are arranged in a flow diagram as illustrated in Fig. 16.4.

Drug concentrations in the various tissues are predicted by organ tissue size, blood flow and experimentally determined drug tissue–blood ratios. Second, blood flow, tissue size and the drug tissue-blood ratios may vary due to certain pathophysiologic conditions. Thus, the effect of these variations on drug distribution must be taken into account in physiologic pharmacokinetic models. The model shows that

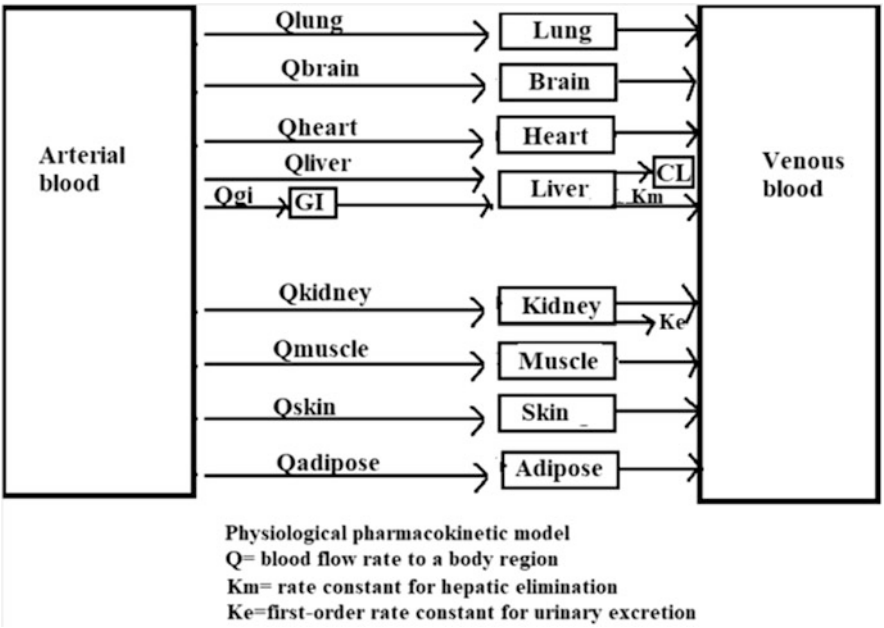


Fig. 16.4 Schematic representation of physiological model

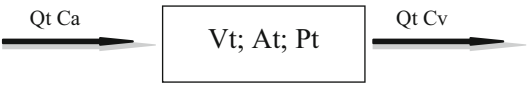
adipose tissue accumulates drugs slowly because of low blood supply and is classified as (slowly equilibrating tissues). In contrast, vascular tissues, like the lung, equilibrate rapidly (rapidly equilibrating tissues) with the blood and start to decline as soon as the drug level in the blood starts to fall. The physiologic pharmacokinetic model provides a realistic means of modelling tissue drug levels. The real significance of the physiologically based model is the potential application of this model in the prediction of human pharmacokinetics from animal data. Unfortunately, the simulated tissue levels cannot be verified in humans because drug levels in tissues are not available. The common representation of a physiological model is shown in Fig. 16.4. Major tissues/organs are represented by compartments from which blood flows carry a drug into and out of tissue/organ. The rate of drug presentation to a particular tissue or organ is dependent upon the rate of perfusion of blood to the tissue or organ and the permeability of the drug is dependent on its partition coefficient between blood and tissue components. Thirteen compartments such as lungs, liver and kidney get maximum blood inflow so are present at the top, followed by other highly perfused organs termed as (HPT) followed by organs which are poorly perfused by blood (PPT) (Gerlowski and Jain 1983; Winter 2004).

Once the selection has been made, the kinds of information required by the model can be classified as (1) anatomical (e.g. organ and tissue volumes), (2) physiological (e.g. blood flow rates and enzyme reaction parameters), (3) thermodynamic

(e.g. drug-protein binding isotherms) and (4) transport (e.g. membrane permeabilities).

Body regions can usually be viewed as consisting of a large number of a single type of cell randomly distributed in the interstitial fluid and supplied with blood by a capillary. This representation is often further simplified, by subdividing the region into three homogeneous fluid compartments: the capillary blood volume, the interstitial water and the intracellular space. Most physiological pharmacokinetic models developed to date are based on the assumption that drug movement within a body region is much more rapid than the rate of delivery of drug to the region by the perfusing blood. In other words, the exchange of drugs between capillary blood and interstitial water is considered to be very rapid and the cell membrane is considered to be very permeable to the drug.

The physiologic pharmacokinetic model can be described for a single well-mixed tissue compartment as



$$\text{Mass} - \text{balance equation} : \frac{dA}{dT} = V\frac{dC}{dt} = QtCa - QtCv \qquad (16.1)$$

Where Qt = tissue blood flow, Cv = venous blood concentration, Ca = arterial blood concentration, Pt = tissue/blood partition coefficient, Vt = volume of tissue and At = amount of chemical in tissue.

The physiology-based pharmacokinetic models (PBPK) models are complex and depend upon various parameters. Generally, these parameters represent the combined effects of not only the drug that is administered but also the subject to which the drug is administered. The simple PBPK models have various limitations which are quite a challenging activity for a variety of reasons including:

- Lack of complete knowledge of dynamics, whose features change with time, and are differentially expressed by various species, and within single species by the different individuals.
- Lack of specific and detailed mathematical formulation to acknowledge the experimental data.
- An increasing number of parameters grows with the equation complexity and this may lead to unmanageable formulations.
- Furthermore, several parameters introduce specificity and this reduces the model's flexibility to describe different systems.

This led to the development of pharmacokinetic models with the lowest complexity and at the same time capable of describing the concerned process and representing it with the help of easy mathematical formulas.

16.2.3 Non-compartment Model

The non-compartmental method is based on statistical moment theory and is not dependent on assumptions of a specific compartment model for either drug or metabolite. In fact, this method can be applied to any compartmental model, provided that alinear pharmacokinetics is assumed. The time course of drug concentration in plasma can usually be regarded as a statistical distribution curve.

The route of drug administration does not affect the process and the first three (zero to second) statistical moments are defined as follows:

$$\text{Zero moment AUC} = \text{AUC} = \int_0^{\infty} \text{Cdt} \tag{16.2}$$

$$\text{First moment MRT} = \frac{\text{A} \cup \text{MC}}{\text{A} \cup \text{C}} = \frac{\int_0^{\infty} \text{TCdt}}{\int_0^{\infty} \text{Cdt}} \tag{16.3}$$

$$\text{Second moment :} \quad \text{VRT} = \frac{\int_0^{\infty} \text{T2Cdt}}{\int_0^{\infty} \text{Cdt}} \tag{16.4}$$

where MRT stands for mean resident time and VRT stands for the variance of the mean resident time of a drug in the body. AUC, MRT and VRT are termed as the zero, first and second moment, respectively, of the drug concentration-time-curve. The area under the curve of a plot of the product of concentration and time versus time from zero to infinity is often referred to as the area under the (first) moment curve, AUMC.

The first moment of the blood level-time curve, mean residence time, is the statistical moment analogue to half-life ($t_{1/2}$). It is defined as the average amount of time spent by the drug in the body before being eliminated. The MRT represents the time for 63.2% of the administered dose to be eliminated statistically.

It is evident that statistical moment theory permits a wide range of analyses that, in most instances, will be adequate to characterize the pharmacokinetics of the drug including bioavailability, clearance and apparent volume of distribution etc. It is also useful in determining half-life, rate of absorption and absorption rate constant without the complex procedures of compartment modelling irrespective of the number of compartments. Certain problems are not addressed by this theory; non-linear events are not adequately treated by the statistical moment theory. Statistical moments provide only limited information regarding the time course of drug concentrations; for the most part, we deal with averages.

16.3 Novel Pharmacokinetic Models

One of the major issues of complex PBPK models is to derive certain mathematical parameters to represent and express the process of absorption, distribution, metabolism and excretion in the system. There are certain updated models which inculcate new scientific technologies and methodologies to better describe the characteristics of the drugs in the body.

16.3.1 Lumped and Flexible PBPK Model

There have been certain advantages and limitations of both compartmental and PBPK models. Most of the cases utilize classical compartmental PK or the physiologically-based PK approach independently or in parallel, with little to no overlap or cross-fertilization.

The lumped flexible PBPK model is an approach that establishes the link between mechanistic PBPK models and classical compartmental models. The proposed method has several advantages over existing methods: Perfusion and permeability rate-limited models can be lumped; the lumped model allows for predicting the original organ concentrations, and the volume of distribution at a steady state is preserved by the lumping method as seen in Fig. 16.5 (Nestorov et al. 1998).

The compartments (rectangles) are organs or lumped organ tissues which have similar pharmacokinetic characteristics. In this approach, the researchers have the choice of exclusively selecting the specific organs depending upon their objective of

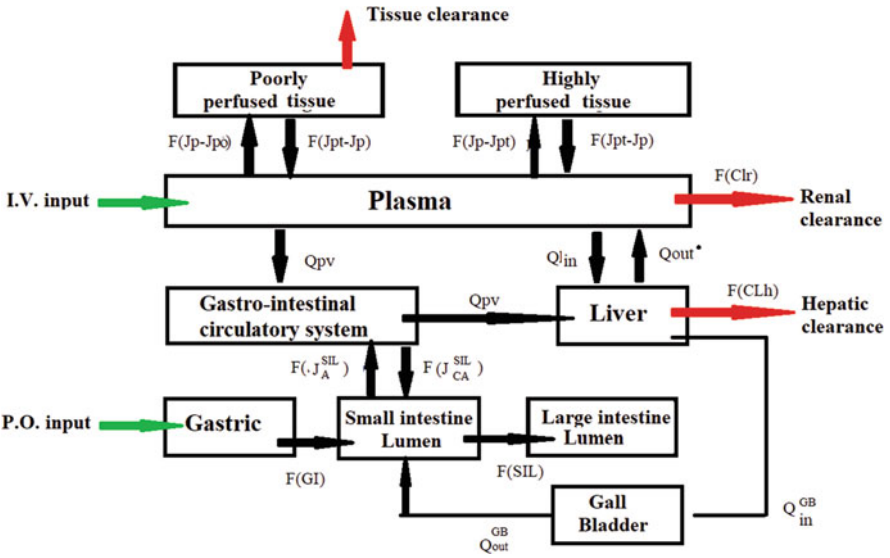


Fig. 16.5 Schematic representation of lumped physiological pharmacokinetic model

study. In most cases, the organs that have a primary role in the ADME paths are considered, while those that are merely distribution sites are lumped into a single compartment. A case where highly perfused organs (HO) and the poorly perfused tissues (PT) compartments, which gather the organs and tissues that are not explicitly represented by a dedicated compartment. The difference between HO and PT compartments is linked to the blood vessel perfusion of the single organs/tissues based on the assumption that the higher the perfusion, the easier the drug transport. This model, contrary to most of the PBPK literature models, considers only the liquid fraction of blood, i.e., plasma. This is convenient because the plasma consists mostly of water that acts as a solvent and suspending medium, and transports the drug to different organs and tissues (Brochot et al. 2005; Di Muria et al. 2010).

The gastrointestinal circulatory system (GICS) compartment lumps several vessels from the gastrointestinal tract that transport nutrients and possibly drugs to the liver via portal vein. In addition, GICS allows considering the so-called first-pass effect of orally administered drugs. This is related to hepatic metabolic activity. The portal vein (belonging to the GICS compartment) conveys drugs right after intestinal absorption to the liver where, depending on the specific active principle undergoes a metabolic action, which produces a partial loss of the administered dose. The liver compartment is considered individually as it has both anatomical and physiological relevance. At the anatomical level, it receives a large amount of the administered drug from both the systemic circulation (via the hepatic artery) and the intestinal region (via the portal vein). At the physiological level, it plays an important role in the drug metabolism using the hepatocyte's action. The gastrointestinal region is schematized into three compartments: the gastric (GL), small intestinal (SIL) and large intestinal (LIL) lumina, and characterizes the entire drug absorption process in case of oral administration, starting with the ingestion into the GL, up to faecal excretion from LIL. Finally, an additional compartment, the gall bladder, allows modelling the bile enterohepatic circulation process, which assists the digestion of lipids.

This periodic process of accumulation and release produces a characteristic effect of multiple drug concentration peaks in the PK profile of some drugs, e.g., sorafenib, erythromycin, ampicillin and phenolphthalein (Shiffman et al. 1990; Roberts et al. 2002).

The lumped PBPK model introduces and considers the issue of the binding process between drug molecules and plasma proteins (i.e. albumin, lipoproteins and globulins). Every drug has its tendency to bind specific proteins, thus reaching a dynamic equilibrium. When a drug is bound to a protein, it is confined within the plasma, as the drug-protein ensemble cannot diffuse through the endothelium of blood vessels. A specific parameter (R) accounts for a kind of drug-protein passive nature in the blood compartment.

In summary, the proposed lumping scheme comprised the following steps:

1. Simulate the whole-body PBPK model to predict the concentrations C_{tis} in all organs and tissues.

2. Plot the normalized concentrations and identify the groups of organs/tissues with similar normalized concentration-time profiles.
3. For each group of organs/tissues L, determine the lumped volume, blood flow and partition coefficient.
4. The process of simulation is applied to the lumped model and the lumped concentration (CL) for all groups of organs/tissues is determined.
5. The original tissue concentration (C_{tis}) is determined from CL for each organ/tissue group.

16.3.2 Pharmacokinetic Models for Optimizing Nanomedicines

Nanomedicines have been developed for more than four decades to optimize the pharmacokinetics of drugs, especially absorption, distribution and stability in vivo. Unfortunately, only a few drug products have reached the market. One reason among others is the lack of proper PK modelling and evaluation, which impedes the optimization of these promising drug delivery systems. So, it is extremely necessary to determine the biodistribution of nanomedicines in the body. The physical characteristics of nanomedicines are quite different from simple drug molecules due to a variety of reasons including a very high surface area to mass ratio, surface charge and release of activity from the nanosystem. The simple pharmacokinetic models do not take into account the specificity of these nano-drug delivery systems (Alexis et al. 2008).

The parameters that have to be included in the pharmacokinetic model for describing the complete profile of nanomedicines are described in Table 16.1 and shown underneath in Fig. 16.6:

16.3.2.1 Absorption

- In case of absorption, the model should consider the stability of the nanocarrier in GIT and should be suitably included.
- Mucus penetration of NPs is a limiting factor in the case of absorption of a nanomedicine. So, it should be included in the PK model.
- Absorption mechanism and nanoparticle integrity is considered an important parameter to be considered for inclusion in the PK model (Groo et al. 2015).

16.3.2.2 Distribution

- The complete distribution and interaction of NPs with the body tissues must be considered.
- The factors playing a crucial role in distribution parameters must be studied which include size, shape and charge.
- Volume of distribution (V_d) could not explain the distribution pattern of NPs.

The most important information that needs to be utilized for developing an accurate PK model is to consider the dynamic equilibrium that exists between the

Table 16.1 A comparison of ADME Properties and PK models of small molecule drugs and nanoparticles

Subject	Small molecules	Nanoparticles
Molecules to be modelled	Active ingredient and/or Metabolite(s)	• Nanoparticle • Nanoparticle-associated Drug and released drug
Major application	• Prediction of rate of absorption and rate of excretion Food-drug and drug -drug interaction studies affecting ADME • Special population PK Prediction (paediatrics, renal/ hepatic impairment, pharmacogenetics, sex, race, pregnancy, obesity)	• PK prediction and risk assessment • Optimization of formulation. Physicochemical property–ADME relationships • Prediction of in vivo drug release from nanoparticles and correlation with in vivo activity
Transport mechanism incorporated into models	• Absorption and distribution: diffusion and/or active transport by transporters • Metabolism: CYP enzymes and non-CYP enzymes; • Excretion: renal and biliary excretion	• *Absorption*: paracellular Transport, transcytosis and M cell uptake (oral), Macrophage uptake and diffusion (s.c., i.m. or inhalation), lymphatic uptake • *Distribution:*opsonization, MPS uptake, target-mediated disposition, EPR effect, lymphatic transport • *Metabolism*: extracellular Degradation, endocytosis and phagocytosis • *Excretion*: renal and biliary Excretion
Challenges	• Prediction of active transport and non-CYP metabolism • Prediction of patients suffering with renal or hepatic disease with altered pharmacokinetics	• Limited understanding on the transport mechanisms and ADME • Immunogenicity and nanotoxicity affect ADME of nanoparticles • Un equal distribution in tissues • Variability in MPS effect • Insufficient initial model parameters

encapsulated drug, free drug and the free NP. Regular PK models do not consider this approach (Longmire et al. 2008).

16.3.3 Pharmacokinetic Models for Describing Direct Delivery to the Lungs

There are certain conditions and disorders where direct targeting of drugs to the desired tissue is the preferred method and the best example is the delivery of drugs to the lungs. The novel drug delivery system via inhalation is the preferred method for delivering therapeutic aerosols to the respiratory tract. The efficacy of an inhaled

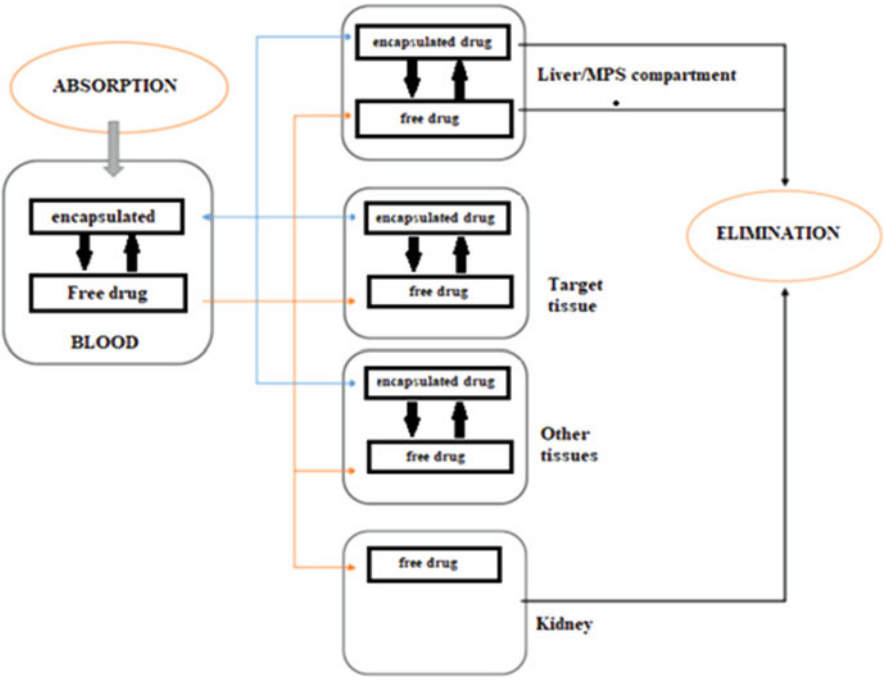


Fig. 16.6 Schematic proposed model adapted for describing pharmacokinetics of nanoparticles and their bio-distribution

therapy depends primarily on the quantity of drug deposited in the lung which in turn depends upon certain factors including formulation characteristics, device characteristics and patient characteristics (Chapman et al. 2011).

The normal physiological models could not assess the chain of clinically relevant aspects which are present in the delivery to the lungs and could correlate and characterize the performance of the device including flow characteristics of the inhaler mouthpiece, powder emptying (i.e. the efficiency by which the powder is released from the capsule after inhalation) and detachment (i.e. the detachment of the active substance particles from the surface of the carrier particles), and physiological parameters such as inhalation rate and airway anatomy.

The Biophysical model is an approach to predict inhaled drug deposition in patients with respiratory diseases and quantitatively investigate sources of variability in the delivery of inhaled drug with the device utilized formulation type, and patient variability. The model uses certain drugs, e.g., Indacaterol and glycopyrronium; and a novel drug delivery system called 'Breezhaler' (DPI), Novartis, Bael, Switzerland. The 'Biophysical model' is a complex combination of integrated computational fluid dynamics, in vitro experiments, and in vivo lung measurements (Fig. 16.7). The model was utilized to assess certain important parameters, namely flow characteristics of inhaler, powder emptying, detachment of active from carrier particles, and the effect of physiological variables including inhalation rate, airway

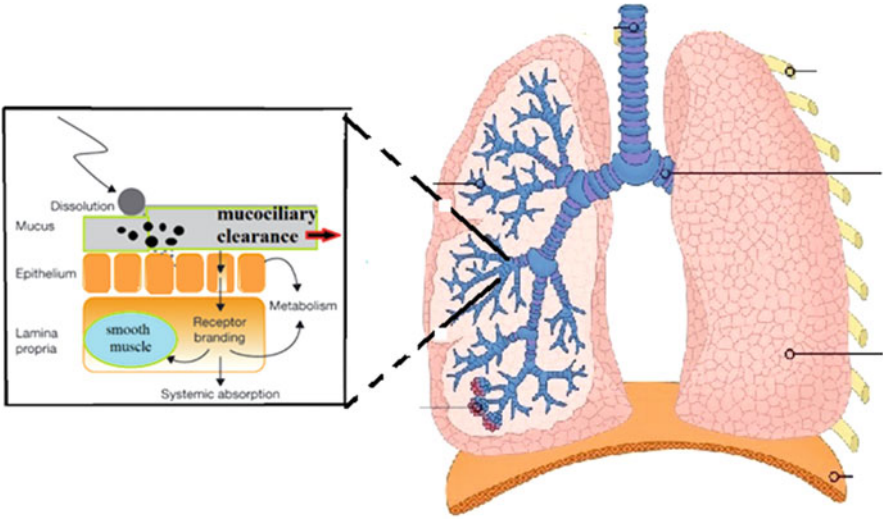


Fig. 16.7 Diagrammatic presentation of biophysical model for direct delivery to lungs

anatomy, inclination angle etc. To compute the aerodynamic particle size distribution and the drug dose delivered into the patient's lungs, 3D computational models of the human oropharynx were used with the inhaler mouthpieces attached. The anatomical model utilized for the process is the 'Alberta mouth throat model'. The biophysical lung model utilizes integrated computational fluid dynamics in combination with in vitro aerosol and in vivo lung measurements (Grgic et al. 2004; Dolovich et al. 2019).

16.3.4 Hybrid Pharmacokinetic Model for Characterization of PK Parameters in Tumours

The current era is mainly utilizing and trying to formulate molecular and targeted anticancer therapeutics. It is very essential to understand drug dynamics in the tumour. It is very advantageous to be able to relate drug concentrations in tumours to corresponding biological endpoints. A novel physiologically based hybrid pharmacokinetic model is developed to predict human tumour drug concentrations. Such models consist of a forcing function, describing the plasma drug concentration-time profile, which is linked to a model describing drug disposition in tumours. The hybrid models are originally derived from preclinical data and then scaled to humans. Integral to the scale-up procedure is the ability to derive human forcing functions directly from clinical pharmacokinetic data (Dogra et al. 2020).

Translation of these preclinical hybrid models to humans used a Monte Carlo simulation technique that accounted for intra-subject and inter-subject variability. Different pharmacokinetic endpoints, such as the AUC tumour, are extracted from

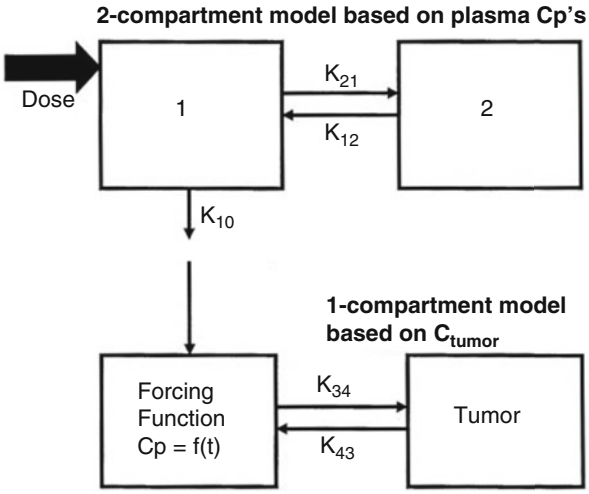


Fig. 16.8 Schematic representation of hybrid pharmacokinetic model having two-compartment plasma disposition characteristics and one compartment tumour model

the simulated human tumour drug concentrations to show how the predicted drug concentrations might be used to select drug-dosing regimens. It is believed that this modelling strategy can be used as an aid in the drug development process by providing key insights into drug disposition in tumours and by offering a foundation to optimize drug regimen design. The schematic representation of the hybrid model is shown in Figs. 16.8 and 16.9 (Gallo et al. 2004).

16.3.5 Multiorgan-on-a-Chip: A Systemic Approach to Model Inter-Tissue/Organ Transfer

The delivery of drugs follows a specific sequence and consequences in the body which is characterized by the body itself. The small intestine absorbs the (digested) substances, the liver metabolizes them, they are then delivered to target organs via the blood circulation and the kidney excretes corresponding waste products. This complex process of absorption/distribution/metabolism/excretion/toxicity (ADMET; affects the fate, distribution, efficacy and possible toxicity of exogenous substances). There is complex communication between organs and systems at the chemical and neuroglia levels. Together, this systemic and cross-organ communication is the key to deciphering and emulating the temporal processes involved in physiological functions.

But in vivo models suffer from numerous limitations: high experimental costs, limited throughput, ethical concerns and differences in genetic background. More importantly, they exhibit large physiological differences in terms of drug effects and/or disease phenotypes compared with humans, which explain the frequent

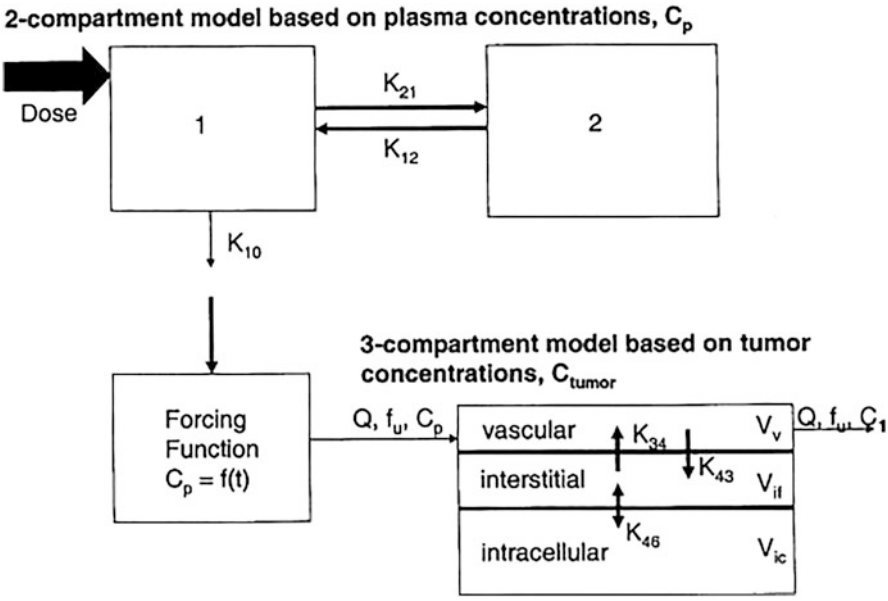


Fig. 16.9 Schematic representation of hybrid pharmacokinetic model having two-compartment plasma disposition model and three-compartment tumour model

failure of clinical trials. Overall, animals do not allow an analysis of inter-organ crosstalk, determination of quantitative pharmacokinetics (PK) or prediction of ADMET parameters, as recently highlighted. Therefore, advanced in vitro approaches incorporating a systemic dimension and multiple organs must be developed to faithfully emulate human health and pathophysiology.

16.4 Conclusion

In drug discovery and preclinical development, pharmacokinetic modelling is frequently used to optimize the selection of drug candidates based on in silico and in vitro data that are likely to have the desired in vivo pharmacokinetic properties. After entry into clinical development, there is a shift from mechanistic to empirical modelling and the clinical drug development does not directly benefit from the effort that has been made to develop a PBPK model in the preclinical stage. Thus, approaches that can establish links between the mechanistic PK models and the empirical models are highly desirable to bridge the gap between preclinical and clinical model development.

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