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Physiologically Based Pharmacokinetics: A Simple, All Purpose Model

Michela Di Muria, Gaetano Lamberti,* and Giuseppe Titomanlio

Dipartimento di Ingegneria Chimica e Alimentare, Università degli Studi di Salerno, via Ponte don Melillo, 84084 Fisciano (SA), Italy

To predict the drug hemeatic levels after administration is a goal of great interest in the design of novel pharmaceutical systems and in therapies management. The most reliable approach in pharmacokinetic modeling consists in analyzing the physiology of the living beings and in describing tissues and organs as different biochemical reactors. These models have been identified as physiologically based pharmacokinetic models (PBPK). They can be very detailed in the description, but, in this case, they also claim for the knowledge of an high number of parameters which are difficult to be determined by experiments. In this work, a review of the most complete PBPK models proposed in literature was performed, and a novel PBPK model was developed and validated by comparison with in vivo data available in the literature. The appeals of the novel model are its simplicity and the limited number of parameters required. Last but not least, it was proved able to predict the hemeatic drug levels after different kinds of administrations (intravenous injection, oral assumption of delayed release tablets).

1. Introduction

The administration of a drug in the human body can have the desired effects if the concentration obtained in the body is within the therapeutic range (i.e., above the minimum effective concentration (MEC) which causes positive effect and below the minimum threshold value (MTV) which causes negative effects). The prediction of the drug concentration in the blood, tissues, and organs is the goal of the pharmacokinetic modeling. The approaches to the modeling of the physiological phenomena can be different on the basis of the details used. More details are taken into account by the description as closer to the phenomena taking place in the body the description is.

The processes that a drug follows after the administration are absorption, distribution, metabolism, and excretion (ADME); these processes determine the evolution of the drug concentration in the body, which can be experimentally monitored. The in vivo experiments are the most important source of information for pharmacokinetics but obviously they are very expensive and time-consuming. The in vitro experiments, other useful supports, are easier and do not have legislation constraining policies to be observed (ethic requirements). The possibility to avoid measurements carried out directly on the living systems makes the pharmacokinetic analysis less onerous; the availability of a model which can predict the fate of a drug without performing experiments on humans or animals is a great ambition in pharmacology and it would be a significant achievement for industrial and clinical purposes.

The aim of this work is to develop and validate a physiologically-based pharmacokinetic model which describes the physics of ADME phenomena with a reasonable number of inputs and of simple usage. This model is concerned with stimulating the following cases of administration: the intravenous injection, by which the drug immediately enters the systemic circulation, and the oral assumption of pharmaceutical formulations with different release rates, accounting for the gastrointestinal tract adsorption delay before the drug reaches the blood. The possibility to describe also the cases of oral assumption of dosage forms with delayed release is an important feature of the model because of the fact that the use of these administration vehicles is increasing thanks to the patients compliance.

1.1. Factors Influencing the ADME Phenomena. The several occurrences that a drug undergoes in the body are of the same kind of the phenomena (transport phenomena, chemical and physical equilibrium phenomena) commonly encountered in the chemical engineering practice. Therefore, they can be analyzed using the same theoretical tools.

The route of administration, the physical and chemical properties of the substance, the characteristics of the dosage form and the physiological conditions are the factors with the most important effects on the entity and the rate of the ADME phenomena. In the time evolution of the drug levels within the human body also the age, the gender, and the weight can have an significant role. The **absorption** of a drug is rapid and complete in the case of intravenous injection, while it is generally delayed and incomplete in the case of oral assumption. The main mechanisms by which the absorption can take place are passive diffusion, facilitated diffusion, and active transport. The fraction of the drug that overcomes the biological barriers by passive diffusion enhances with the increase of the solubility of the drug (which depends on the pH, the drug form crystalline/amorphous, the crystal size) in the gastrointestinal fluids, with the increase of the affinity of the substance for the phospholipids that constitute the living membranes, with the decrease of the drug molecular weight, with the decrease of the pK_a of the species, and with the increase of the residence time in the gastrointestinal tract. The rate of this phenomenon improves with the increase of the diffusion coefficient of the drug and with the decrease of the dimensions of particles which constitute the pharmaceutical formulation; it also varies with the composition of the dosage form. The facilitated diffusion and the active transport are more sophisticated absorption mechanisms in which a carrier is involved.

The **distribution** of a drug is more rapid if the rate of absorption increases: in the case of intravenous injection the time of appearance of the drug in the tissues and organs is more brief than in the case of oral assumption. The mechanisms by which a drug is extended to tissues and organs are the same by which the substance passes the gastrointestinal mucosa. Therefore, in the passive diffusion, a higher affinity for the constituents

* To whom correspondence should be addressed. E-mail: glamberti@unisa.it.

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of the biological membranes causes an increase in the entity and in the rate of the phenomenon. The amount of the drug which can be contained in a tissue or an organ rises as the real volume of the tissue or organ increases and as the fraction of the species bound to the plasma proteins decreases; the higher is the blood perfusion in the tissue or organ, the faster is the drug reaching and leaving it.

The **metabolism** of a drug is strongly dependent on the route of administration: if the substance is taken by intravenous injection, it is introduced in the systemic circulation and directly distributed to tissues and organs, whereas, if it is taken by oral assumption, it undergoes the first-pass effect with which a fraction of drug is metabolized before reaching the systemic circulation. The mechanisms of the metabolism are the different enzymatic reactions which occur mainly in the liver but also in other tissues and organs such as the intestinal mucosa and the kidneys; the products are polar and hydrophilic compounds which can have or not therapeutic (in some cases dangerous) effects. The fraction of the drug metabolized rises with the increase of the number of metabolizing sites and with the increase of the intrinsic clearance of the enzymes; the rate of the biotransformation increases also with the decrease of the fraction of the substance bound to plasma or tissues proteins.

The **excretion** of a drug takes place by two main routes, the liver and the kidneys, which produce the bile and the urine, respectively. The mechanism of the substance removal from the body depends on its molecular weight: compounds with $MW > 500$ Da are generally excreted in the bile, the others in the urine. The liver metabolizes the species by secretion, the kidneys by filtration (passive transport) and secretion (active transport). The more hydrophilic are the substances administered, the higher is the amount of the percentage of the dose excreted; the more ionized, made up of polar substituents, and unbounded to plasma and tissues proteins are the drug molecules, the higher is the rate of elimination.

The effects of the parameters with interindividual variability are not univocal and often complex; they are not considered in the development of our model, which wants to be a general and not onerous tool for the interpretation of the behavior of the body toward the administration of a drug and for the prediction of drug levels within the various regions of the body.

1.2. Pharmacokinetic Modeling. The pharmacokinetic predictions can be carried out after a model of the physiological processes, which takes into account the variability due to the factors outlined above, has been prepared and implemented into a simulation code. Modeling and simulation are actions commonly performed by the engineers. Such actions are not new in the development and the drug delivery, but recently a trend to move from the descriptive one to the predictive role of the pharmacokinetic models has emerged.

The approaches which can be used in the description of the fate of a drug within the body are two: compartmental and noncompartmental. These kinds of models are designed with different criteria and in principle not all of them can be predictive. The noncompartmental approach consists in finding the fitting mathematical law for the available experimental data, therefore it does not propose a physical interpretation of the events that happen in the body. The compartmental approach is based on the schematization of the body by a system of interconnected volumes, the compartments, which can be easily identified by a chemical engineer as chemical reactors (usually continuous stirred) or as physical contacting units. Two major groups of compartmental models can be used in pharmacokinetic modeling: the mechanistic and the physiologically based ones. The first category includes models in which the compartments do not represent necessarily anatomical units. The last one includes the models in which each compartment is representative of a tissue or an organ of the body and in which the interconnections between the compartments reproduce the effective ones between tissues or organs. Both the mechanistic and physiologically based models offer a description of the reality of the processes that a drug undergoes in the body, but the first is less accurate than the last; the physiologically based approach uses a mathematical description closer to the actual physical phenomena; therefore, the predictions could be more truthful.

In this work the approach we use is a semiphysiologically based one: our model is made up by some reactors corresponding to anatomical units and some reactors corresponding to groups of tissues and/or organs. The approach has been chosen having the purpose of producing a model with an easy mathematical structure, not onerous to be applied, but with a firm physical basis.

2. State of Art

In the existing literature there are several examples of pharmacokinetic compartmental models. The most important, referenced by a lot of researchers in their publications, are the first whole-body physiologically based pharmacokinetic model by Jain et al.,[1,2] relevant to simulate cases of intravenous injection, and the model by Yu, Amidon et al.,[3] thought to simulate cases of oral administration. The publications by Jain et al. and Yu, Amidon et al. have inspired some other important literature works.

2.1. The Model by Jain et al. The model by Jain et al.[1] is the first whole-body physiologically based pharmacokinetic model. It is based on the schematization of the rat body into 21 compartments, each representative of an anatomical constituent. The mathematical structure of the model is made up by a system of 38 coupled ordinary differential equations (ODEs), which have to be solved with the initial conditions that all the concentrations, but the plasma concentration, at the initial time of the administration are equal to zero. The simultaneous resolution of the model equations, with the initial conditions, require the knowledge of the 98 model parameters (38 real volumes, 17 blood flows, 19 mass transfer coefficients, 19 binding constants, and 5 clearances). An application of the whole-body physiologically based model, in a case of intravenous injection of zinc sulfate in rats, was carried out by Jain et al. The pharmacokinetic profiles found in the tissues and organs by fitting the model parameters listed below agreed with the experimental trends, and the average errors between the measured and the model concentrations equaled 10% over a 3 week simulation period.[1]

The problem in the use of the model by Jain et al. is the high number of model parameters (37 on 99) which have to be fitted; thus, it is very difficult to adopt the model for predictive purposes. Furthermore the model by Jain et al. refers only to the case of intravenous administration; the model was not pertinent to simulate cases of oral administration. For these reasons the complete whole-body physiologically based model by Jain et al.[1] has not been adopted in the literature or by the authors themselves.

2.2. The CAT Model by Yu, Amidon et al. The complete model by Yu, Amidon et al. is defined as the "Compartmental Absorption and Transit" (CAT) model.[4,5] The schematization of the gastrointestinal tract was made up by one compartment standing for the stomach, seven for the small intestine, one for the colon, and one for the plasma.[3] In this schematization, sites

of distribution are not included. The mathematical structure of the model is made up by 10 coupled ordinary differential equations (ODEs), which have to be solved with initial conditions (on the fraction of the dose in the gastrointestinal tract and on the plasma concentration) to characterize the time profiles of the drug levels in each compartment.[3] The simultaneous resolution of the system of the model equations and the appropriate initial conditions require the knowledge of the eighteen parameters (one gastric emptying rate constant, one transit rate constant - assumed equal for all the compartments -, seven absorption rate constants, seven degradation rate constants, one elimination rate constant and one volume of distribution - both referred to plasma -).

The CAT model was applied to simulate cases of administration in humans of drugs both in immediate release formulations (cefatrizine,[3] atenolol,[6] bretylium,[5] sotalol[5]) and in controlled release formulations (metoprolol, nifedipine, propranol, atenolol)[5] and also of drugs with low solubility or low permeability (digoxin, griseofulvin, panadiplon).[7] In the applications of their model, Yu, Amidon et al. showed a satisfying agreement between the experimental data and the predictions (made with values of parameters taken from the existing literature) of the total fraction of dose absorbed.[6] The main drawback of the CAT model is the fact that the model can be only applied in the case of oral administration.

2.3. The Simplified Models Inspired by Jain et al. A high number of parameters that require estimation in the model by Jain et al. was the reason that in subsequent literature there was an attempt to simplify the entire model by those who wanted to use it.

An entire research program was dedicated to this purpose by Nestorov et al.[8−12] They defined the following algorithm to identify the best lumped model: on the basis of their time constants, to group tissues and organs obtaining some competing lumped models; to perform a global sensitivity analysis to find the parameters with the most important effects on the pharmacokinetic profiles; to select only the simplified models with the same mean and the variance of the arterial concentration time profile obtained by the complete model. The comparison between the performances of the simplified models with those of the complete model helped to choose the more efficient. A "lumped" model made up by six compartments was proposed and applied in a case of intravenous injection of barbiturates in rats,[10] but without good correlation with experimental data. To our knowledge, a "lumped" model able to give satisfying predictions of the experimental data is still lacking in the existing literature.

2.4. The ACAT Model Inspired by Yu, Amidon et al. The model by Yu, Amidon et al. was the starting point for the work of the researchers of the society *Simulations Plus, Inc.*, that developed the "Advanced Compartmental Absorption and Transit" (ACAT) model.[13,14] This model is implemented into simulation software, *GastroPlus*. The schematization of the body on which the model is based includes a lot of compartments. The number of the equations and the respective boundary conditions are not accessible because *GastroPlus* is covered by copyright.[13] The complexity of the schematization and of the features of the software still suggests that this number is very high.

GastroPlus was tested as an in-silico tool for the prediction of the effects of the physiological conditions on physicochemical parameters of some therapeutic substances[15,16] and of the resulting time profiles of the drugs plasma levels.[17−19] Pharmacokinetic studies carried out by different authors, which used the simulation program *GastroPlus*, showed that satisfying predictions of the ADME phenomena were possible only by a lot of careful in vitro and in vivo measurements.[20]

2.5. Some Observations on the Existing Models and on the Aim of the Work. All the existing pharmacokinetic models have some drawbacks: The model proposed by Jain et al. requires the knowledge of too many parameters (a great number of which has to be obtained by fitting) and, furthermore, it cannot be applied when the administration route differs from the intravenous; the model by Yu, Amidon et al. can be applied only when the administration route is oral; the applications of the simplified models inspired by Jain et al. have shown that they do not represent valid substitutes to the first whole-body physiologically based model; the ACAT model needs a high number of parameters, a lot of which have to be determined by experimental both in vitro and in vivo measurements.

The need of a model based on the actual physiological cycle of individuals, which can take into account the possibility of dosage by different routes, which can be applied without requiring the estimation of a large number of parameters (only more significant should be selected) and, possibly, not by fitting, has propelled our work.

In a recent paper, Siepmann and Siepmann[21] pointed out the need for a "combination of mechanistic theories describing drug release out of the delivery systems with mathematical models quantifying the subsequent drug transport within the human body in a realistic way". Their paper was focused on the approaches currently adopted to solve the first part of the problem (the drug release out of the delivery systems). The present paper could be seen as a short review of the work done in the other part of the problem (the drug transport/and fate in the body) and a proposal for a full, even simple, model for the pharmacokinetic studies.

3. Modeling

3.1. The Novel PBPK Model. The PBPK model developed in this work was based on a simple representation of the body, reported in Figure 1.

Each of the blocks represents an organ/a tissue/a fluid of the body or a group of them: the gastrointestinal tract is split into the stomach, the small intestine and the large intestine; the gi.c.s block for the gastrointestinal circulatory system; the liver block for the hepatic compartment; the plasma block for the blood and the largely perfused tissues and organs; the tissues compartment for the scarcely perfused tissues and organs. The continuous arrows represent the mass flow rates between the compartments. The dashed arrows represent the drug inlets after administration by intravenous or oral route: in the case of intravenous injection (i.i.), the only dashed arrow which needs to be considered is that entering the plasma compartment, while, in the case of oral assumption (o.a.), the dashed arrows which need to be considered are those entering the gastric (from ingestion to gastric emptying), the small intestine (from gastric emptying to small intestine emptying), and the large intestine (from small intestine emptying to large intestine emptying) lumen.

The PBPK model consists of the mass balance equations on the compartments and of the initial conditions which are necessary for solving them. The assumption made in doing mass balances are that the blocks can be likened to continuous stirred reactors and that the mechanism of drug transport across biological membranes (such as the gastrointestinal walls and

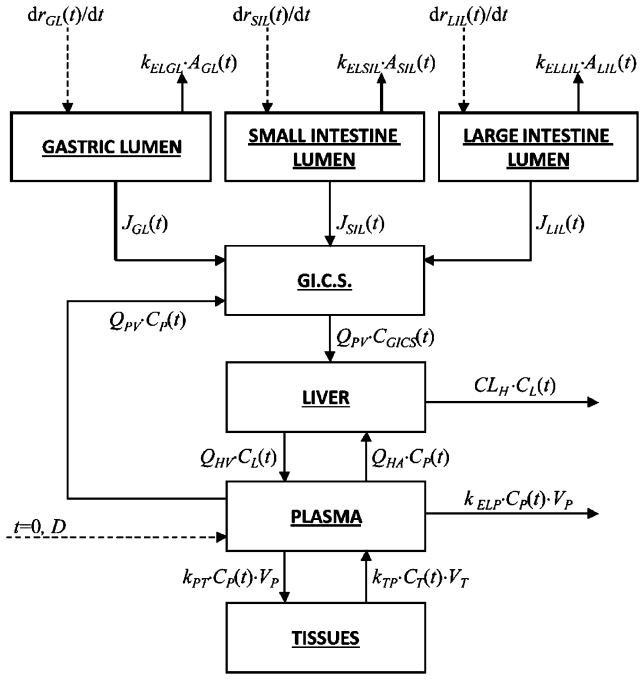

Figure 1. Schematic of the novel PBPK model proposed in this work.

the blood vessels walls) is the passive diffusion. The PBPK model mass balance equations are indicated in the Table 1.

The following definitions pertain to Table 1: $A_{GL}(t)$, $A_{SIL}(t)$, and $A_{LIL}(t)$ are the time evolutions of the drug contents (masses) in the gastric, small intestine, and large intestine lumen, respectively; $C_{GICS}(t)$, $C_L(t)$, $C_P(t)$, and $C_T(t)$ are the time evolutions of the drug concentrations in the gastrointestinal circulatory system, in the liver, in the plasma, and in the tissues compartments, respectively; $G(t)$, $S(t)$, and $L(t)$ are the time functions which activate the drug release during the transit of the pharmaceutical form in the gastric, small intestine, and large intestine lumen, respectively; $r(t)$ is the time evolution of the in vitro measured drug release (in the mass balances, the time derivative of $r(t)$ is equal to zero in the case of intravenous injection or in the case of oral assumption of immediate release formulations because the drug release is instantaneous, while it can be calculated from the in vitro drug dissolution data in the case of oral assumption of delayed release formulations); $J_{GL}(t)$, $J_{SIL}(t)$, and $J_{LIL}(t)$ are the time evolutions of the mass flow rates of the drug exchanged between the gastrointestinal cavities and the gastrointestinal circulatory system, estimated by the following relationship (in which the subscript "*i*" indicated the generic tract of the gastrointestinal lumen and it can be equal to "G", "SI" or "LI"):

$$J_{iL}(t) = k_{AiL} V_B \left(\frac{A_{iL}(t)}{V_B} - \frac{C_{GICS}(t)}{R_{GICS}} \right) \quad (1)$$

Also, V_B is the volume of the bolus crossing the gastrointestinal tract; R_{GICS} is the drug partition coefficient in the gastrointestinal circulatory system; k_{AGL}, k_{ASIL}, and k_{ALIL} are the kinetic constants of absorption from the gastric, small intestine, and large intestine lumen, respectively; k_{ELGL}, k_{ELSIL}, and k_{ELLIL} are the kinetic constants of elimination (metabolism and excretion) from the gastric, small intestine, and large intestine lumen, respectively; V_{GICS} and V_L, are the physical volumes of the gastrointestinal circulatory system and liver, respectively; V_P and V_T are the distribution volumes of the plasma and the tissues compartments, respectively; Q_{PV}, Q_{HA}, and Q_{HV} are the blood volumetric flow rates of the portal vein, the hepatic artery, and the hepatic vein, respectively; CL_H is the hepatic clearance; k_{ELP} is the kinetic constant of elimination from the plasma compartment; k_{PT} and k_{TP} are the mass transfer coefficients, respectively, from the plasma compartment to the tissues one and from the tissues compartment to the plasma one.

The PBPK model was conceived to be applied in the cases of both single and multiple administrations.

To simulate the drug concentration evolution in the body, besides the in vitro drug dissolution profile ($r(t)$, which is needed only in the case of oral assumption of delayed release formulations), the kinetic constants, the partition and mass transfer coefficients, the physical and distribution volumes, and the volumetric flow rates listed below, the residence time in the gastric (t_{GL}), small intestine (t_{SIL}) and large intestine (t_{LIL}) lumen are required, together with the times (t_{Aj}) at which each of the potential administrations begins.

The PBPK model initial conditions have to be diversified on the basis of the route of administration, the kind of pharmaceutical form and the frequency of the administrations. The following cases have to be specified:

1. Single Intravenous Injection. The initial drug masses and concentrations in the compartments are all equal to zero, with the exception of the initial concentration in the plasma compartment which can be considered equal to the ratio of dose administered to plasma compartment volume.

2. Single Oral Assumption of an Immediate Release Pharmaceutical Form. The initial drug masses and concentrations in the compartments are all equal to zero, with the exception of the initial mass in the gastric lumen, which can be considered equal to the dose.

3. Single Oral Assumption of a Delayed Release Pharmaceutical Form. The initial drug masses and concentrations in the compartments are all equal to zero.

4. Multiple Intravenous or Oral Administrations. In the compartments, the drug masses and concentrations at the time of the *j*th administration are those obtained by effect of the previous $(j - 1)$th administration.

In these different cases of administration, the drug masses in the gastric, small intestine, and large intestine lumen need to be updated after the emptying of each of the gastrointestinal cavities: when the drug leaves one of the gastrointestinal compartments to enter another, the drug mass in the first compartment becomes equal to zero, while the drug mass in the last compartment becomes equal to the sum of the drug masses which were in the two compartments immediately before the emptying of the first one.

Summarizing, the novel PBPK model is made up of seven ordinary differential equations (ODEs) with 22 physiological and pharmacokinetic parameters. The resolution of the equations with the appropriate initial conditions, which concerns a real case of administration, can be easily carried out numerically by the aid of a calculation software.

3.2. The Procedure for Parameters Estimation. The resolution of the seven model equations can be carried out only after individuation of the values of the 22 model parameters. Therefore, a strategy for determining the values of the physiological and pharmacokinetic parameter was pointed out. The model, in the next section 4, will be validated by comparison with several literature sets of data of drug administration to either rats (section 4.1) or to humans (sections 4.2 and 4.3).

The residence times either in the gastric lumen (t_{GL}), or in the small intestine lumen (t_{SI}) or in the large intestine lumen (t_{LIL}) were obtained from literature experiments. Several tech-

Table 1. Mass Balance Equations of the Novel PBPK Model

compartment	mass balance equation	
gastric lumen	$\frac{dA_{GL}(t)}{dt} = G(t)\frac{dr(t)}{dt} - J_{GL}(t) - k_{ELGL}(t)\,A_{GL}(t)$	(A)
small intestine lumen	$\frac{dA_{SIL}(t)}{dt} = S(t)\frac{dr(t)}{dt} - J_{SIL}(t) - k_{ELSIL}(t)\,A_{SIL}(t)$	(B)
large intestine lumen	$\frac{dA_{LIL}(t)}{dt} = L(t)\frac{dr(t)}{dt} - J_{LIL}(t) - k_{ELLIL}(t)\,A_{LIL}(t)$	(C)
gi.c.s	$V_{GICS}\frac{dC_{GICS}(t)}{dt} = Q_{PV}\,C_P(t) - Q_{PV}\,C_{GICS}(t) + J_{GL}(t) + J_{SIL}(t) + J_{LIL}(t)$	(D)
liver	$V_L\frac{dC_L(t)}{dt} = Q_{PV}C_{GICS}(t) + Q_{HA}C_P(t) - (Q_{HV} + CL_H)C_L(t)$	(E)
plasma	$V_P\frac{dC_P(t)}{dt} = Q_{HV}C_L(t) + k_{TP}C_T(t)V_T - (Q_{HA} + Q_{PV} + k_{PT}V_P + k_{ELP}V_P)C_P(t)$	(F)
tissues	$V_T\frac{dC_T(t)}{dt} = k_{PT}C_P(t)V_P - k_{TP}C_T(t)V_T$	(G)

niques are available for measuring the crossing times; the most widespread technique is the gamma scintigraphy,[22] which has shown the dependency of the duration of the transit in the gastrointestinal tract on many factors: kind of therapeutic substance, dosage form, presence of food or drugs, age, gender, physiology, and possible diseases. Indicative residence times in the human gastrointestinal environment were taken from literature. In the simulation performed with rat physiology (section 4.1), the residence times were the same of those employed in the simulations performed with human physiology (sections 4.2 and 4.3), with the exception of the residence time in the large intestine: t_{SLI} was assumed to be greater in the rat physiology, as experimental evidence suggested a longer permanence in the gastrointestinal lumen.

The kinetic constants of absorption across the gastric walls (k_{AGL}), the small intestine walls (k_{ASIL}) and the large intestine walls (k_{ALIL}) were calculated by using the following definition:[13]

$$k_{Ai} = \frac{P_{EFFi}S_i}{V_i} \tag{2}$$

where P_{EFFi} is the effective permeability in the living systems, S_i is the surface area, and V_i is the volume of the ith part of the gastrointestinal lumen. The P_{EFFi} value can be calculated starting from the measured $P_{Caco\text{-}2}$ value (the value of Caco-2 cells permeability) and employing correlations reported in literature. The S_i/V_i value, which coincides with the $2/R_i$ (R_i is the radius of the ith part of the gastrointestinal lumen) value if the ith part of the gastrointestinal lumen is assumed cylindrical in shape and can be calculated by the in vivo technique of magnetic resonance imaging (MRI)[23,24] or by postmortem[25] analysis with opportune corrections. In the simulation performed with rat physiology, the k_{AGL}, k_{ASIL}, and k_{ALIL} were obtained from previous findings in the literature. In the simulations performed with human physiology, the k_{AG} value was assumed negligible, because of the marginality of the stomach role in the absorption, while the k_{ASIL} and k_{ALIL} values were computed by eq 2 (the intestinal P_{EFF} value was calculated from the available intestinal $P_{Caco\text{-}2}$ value, by using the Sun et al. correlation for drugs undergoing passive transport; the $2/R$ value was calculated by employing medium values for the radii of each intestinal tract).

The liver volume was taken from literature measurements in experimental campaigns. Magnetic resonance imaging (MRI)[23,24,26] has shown that age, gender, and physiology can have important effects on the liver volume; medium values were taken in the simulations performed with both the rat physiology and the human physiology data.

The volumetric flow rate of the hepatic vein (Q_{HV}), the hepatic artery (Q_{HA}), and the portal vein (Q_{PV}) were taken from literature experiments in the simulation performed with the rat physiology[27] and in the simulations performed with the human physiology.[2829] Literature data based on Doppler effect and using ultrasounds[30] were taken for blood flow rates.

The hepatic clearance (CL_H) was calculated starting from its definition:[31]

$$CL_H = Q_{HV}E_H \tag{3}$$

where E_H is the hepatic extraction ratio. The technique of hepatic venous isolation and charcoal hemoperfusion (HVI-CHP) has been recently employed to measure the hepatic extraction ratio of particular classes of drugs.[32,33] In the simulations performed with the rat physiology and the human physiology, these experimental values of E_H were used.

The distribution volume of the less perfused regions (V_T) was evaluated on the basis of literature indications. In the simulation performed with the rat physiology, the V_T value was evaluated by summing the available[1] measured volumes of each less perfused zone. In the simulations performed with the human physiology the V_T value was evaluated by subtracting from the total distribution volume (taken from literature[34]) of the drug, the distribution volume of the more perfused regions (which value was obtained as shown at the end of this paragraph).

In the simulation performed with the rat physiology, the drug partition coefficient (R_{GICS}) in the gastrointestinal circulatory system was obtained by optimization. In the simulations performed with the human physiology, the drug partition coefficient (R_{GICS}) in the gastrointestinal circulatory system was

estimated as the reciprocal of the measured fraction of the drug unbound (f_{UP}) to its proteins.[34]

The volume of the gastrointestinal circulatory system (V_{GICS}) was calculated from the (experimentally available) value of the volume of the portal vein (V_{PV}), by the following relationship:

$$V_{GICS} = \beta V_{PV} \tag{4}$$

where β is a coefficient greater than one (which takes into account the presence, in the gastrointestinal circulatory system, of other blood vessels, besides portal vein). In the simulation performed with the rat physiology, the V_{PV} value was calculated by summing the available volumes of the proximal and the distal tracts[35] of the portal vein. In the simulations performed with the human physiology, the V_{PV} value was calculated, considering that it is cylindrical in shape, from the literature values of its diameter[36] and length.[37]

The volume of the bolus (V_B) in the gastrointestinal tract was approximately estimated in the simulation performed with the rat physiology and also in the simulations performed with the human physiology.

In the simulation of zinc sulfate pharmacokinetics in rats, the k_{ELG} value was considered negligible and the values of k_{ELG}, k_{ELLIL}, and k_{ELLIL}, not negligible because of the important role of the gut in the zinc sulfate metabolism,[38] were obtained by optimization. In the simulation of theophylline pharmacokinetics in humans, the values of the kinetic constants of elimination across the gastric walls (k_{ELG}), the small intestine walls (k_{ELSIL}), and the large intestine walls (k_{ELLIL}) were considered negligible, because of the facts that the main site of theophylline weak metabolism and excretion is the liver[38] and the main sites of its excretion are kidneys.[34] In the simulation of diltiazem pharmacokinetics in humans, the k_{ELG} value was considered negligible, while the values of k_{ELSIL} and k_{ELLIL}, not negligible because of the relevant role of the gut in the diltiazem metabolism,[38] were assumed equal to those of rabbits, which are available in the literature.[39]

In all the simulations performed, the mass transfer coefficient (k_{PT} and k_{TP}) were obtained by fitting the experimental data with a two-compartments model, previously developed.[40] In all the simulations performed, the kinetic constant of elimination from the more perfused regions (k_{ELP}) and the distribution volume of these zones were obtained by fitting the experimental data with the novel PBPK model.

4. Results and Discussion

4.1. Administration of Zinc Sulfate in Rats. The whole-body physiologically based pharmacokinetic model proposed by Jain et al.[1] was proposed and tested by the authors to describe the fate of the zinc sulfate in rats, administered by intravenous injection. The model is described in section 2.1. It is worth noticing that the model is highly descriptive and, of course, it requires a large number of model equations and parameters. Actually, that model involves the solution of 38 ODEs and it needs the specification of 99 parameters, of which 37 are not experimentally accessible. Therefore, the simulation carried out by Jain et al.[1] was able to describe the pharmacokinetics of the zinc sulfate in each physiological compartment (organ), only after a fitting procedure to determine almost forty parameters. Such a model is thus really interesting to describe and then to clarify the behavior of the body, but its predictive ability was not verified.

The model proposed in this work, depicted in Figure 1 and summarized in Table 1, can be used in the description of the rats body behavior after the administration of zinc sulfate. A lumping procedure has been followed: the most perfused tissues (plasma, skin and fur, muscle, intestine and kidneys) were lumped into the "plasma" compartment of the novel model, the less perfused tissues (stomach, spleen, pancreas, bladder, prostate, gonads, fat, bone and marrow, heart, sex organ, brain, heart and thyroid) were lumped into the "tissues" compartment of the novel model; liver and gut lumen remains unlumped. Of course, because of the lumping procedure, it will require much less parameters (22 in place of 99), and it will describe the behavior of the body with less details. Most of the parameters can be estimated by literature, following the procedure depicted in section 3.2. Only five parameters were optimized by fitting against experimental data. All parameters values adopted in the final simulation are summarized in Table 2. Results of the simulation are summarized in Figure 2. The experimental data (calculated from ref 1 by summation of the data for each compartment, following the lumped procedure depicted previously) are the symbols, the continuous lines are the predictions of the model proposed in this work, and the dashed lines are the results of the original model. It is evident that the predictions of the novel model are in good agreement with the data similar to the original model by Jain et al.,[1] which gives a better description of the short-times dose content in the plasma and in the liver. However, it is worth noticing that the model proposed here is a much simpler one, and the predictions in Figure 2 are obtained after the fitting of only five parameters. Therefore, it can be concluded that the model presented here, despite the simplifications which reduce the number of ODE and the number of parameters to about four, properly accounts for relevant phenomena involved in the pharmacokinetics of a drug administered by intravenous injection (i.i.) in rats.

Table 2. Parameters Values for the Simulation of the Administration of Zinc Sulfate in Rats[a]

t_{GL}	0.8 h	k_{AGL}	0.17 h^{-1}	β	2
t_{SIL}	3.2 h	k_{ASIL}	1.00 h^{-1}	k_{PT}	0.58 h^{-1}
V_L	19.55 mL	k_{ALIL}	0.96 h^{-1}	k_{TP}	1.87 h^{-1}
Q_{PV}	5.88×10^2 mL h^{-1}	k_{ELGL}	0.00 h^{-1}	$\boldsymbol{k_{ELSIL}}$	$\boldsymbol{4.32 \times 10^{-3}}$ $\boldsymbol{h^{-1}}$
Q_{HA}	1.20×10^2 mL h^{-1}	V_T	82.75 mL	$\boldsymbol{k_{ELLIL}}$	$\boldsymbol{4.32 \times 10^{-3}}$ $\boldsymbol{h^{-1}}$
Q_{HV}	7.08×10^2 mL h^{-1}	V_{PV}	5.96×10^{-4} mL	$\boldsymbol{k_{ELP}}$	$\boldsymbol{3.60 \times 10^{-4}}$ $\boldsymbol{h^{-1}}$
C_{LH}	0 mL h^{-1}	V_{CGIS}	1.19×10^{-3} mL	$\boldsymbol{V_P}$	**175.3 mL**
t_{LIL}	500 h	V_B	0.1 mL	$\boldsymbol{R_{GICS}}$	$\boldsymbol{10^{-3}}$

[a] The fitting parameters are given in boldface.

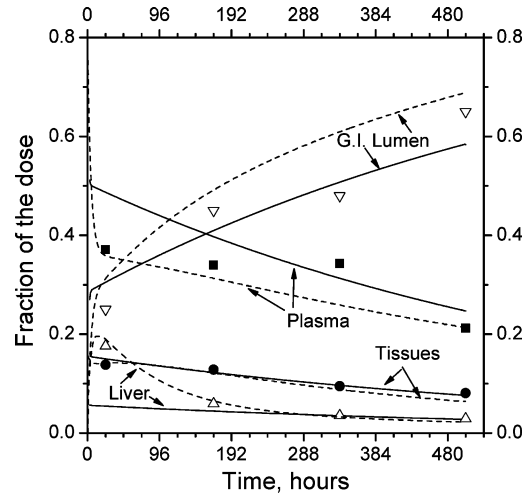

Figure 2. Experimental data (symbols) and predictions (continuous lines, this work; dashed line, Jain et al.[1]) for the administration of zinc sulfate in rats.

4.2. Administration of Theopyilline in Humans. A second step in testing the descriptive ability of the developed model

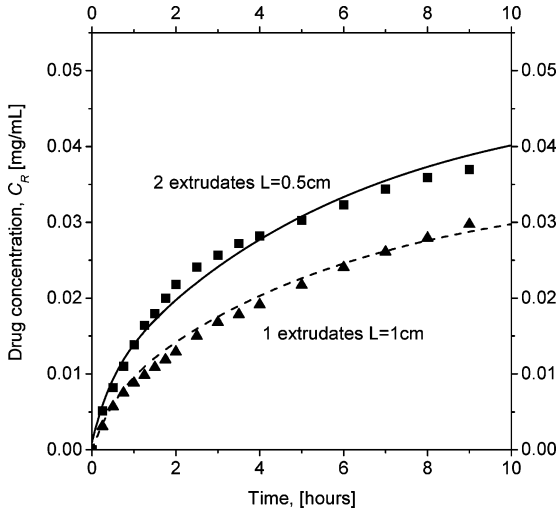

Figure 3. In vitro theopylline release from solid dosage forms. Experimental data, symbols; curves, fitting.

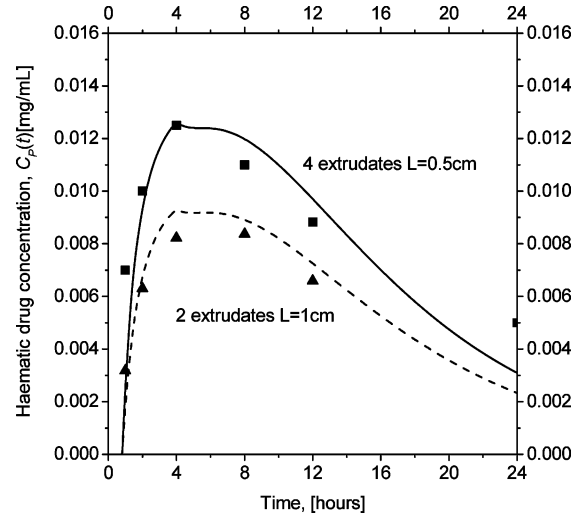

Figure 4. In-vivo hemeatic theopylline concentrations after system administrations. Experimental data, symbols; curves, model predictions.

was to verify if it is able to reproduce the hemeatic concentration evolution observed in humans after the administration of a drug via the oral route. Data on the administration of theopylline to four healthy volunteers by coextrudates produced via the hot-melt technique (an inner hydrophilic core, built of theopylline and PEG with a radius of 0.15 cm; and an outer lypophilic shell, built of theopylline, lactose, and wax, with an outer radius of 0.3 cm) were presented by Quintavalle et al.[41] The authors determined both the in vitro and the in vivo data, that is, the drug concentration evolution in the release medium during laboratory experiments as well as the hemeatic concentration evolution in the volunteers' blood after the administration. The same amount of drug (350 mg) was administered in two different ways, that is, assuming four coextrudates 0.5 cm in length or two coextrudates 1.0 cm in length.

The in vitro release kinetics are reported in Figure 3. The experimental data are the symbols, the curves being the fitting with a suitable time function (they are not model results). Even if the release kinetics could be itself the subject for the modeling (and the authors themselves performed the modeling of the related phenomena[42]), it is not within the scope of the present work to model the drug release and the data were simply fitted with a time function. The administration of four coextrudates causes a faster kinetics, even if the dose is the same, mainly because of the higher surface available for the mass transport phenomena.

The in vivo data are reported as symbols in Figure 4, for both the administrations studied (two coextrudates 1.0 cm in length and four coextrudates 0.5 cm in length). Of course, the faster in vitro release kinetic (four coextrudates 0.5 cm in length) causes a higher hemeatic peak. The pharmacokinetic model proposed in this work was used to simulate the in vivo behavior. The model parameters were estimated as described in section 3.2, and they are reported in Table 3. Of them, only two (k_{ELP}, the kinetic constant of elimination from the plasma compartment, and V_P, the distribution volumes of the plasma) were optimized by fitting the model results to the in vitro/in vivo data, and only the data related to the administration of two coextrudates 1.0 cm in length were used. Therefore, the model could be used to simulate the in vivo behavior due to the administration of four coextrudates 0.5 cm in length. Figure 4 shows also the model predictions for the hemeatic concentration evolution after the administration of four coextrudates 0.5 cm in length, that is, a simulation carried out without any optimizing parameter. It is

Table 3. Parameters Values for the Simulation of the Administration of Theopylline in Humans[a]

t_{GL}	0.8 h	k_{AGL}	0 h^{-1}	β	2
t_{SIL}	3.2 h	k_{ASIL}	2.02 h^{-1}	k_{PT}	3.6×10^{-3} h^{-1}
V_L	1.5 L	k_{ALIL}	1.01 h^{-1}	k_{TP}	3.6×10^{-3} h^{-1}
Q_{PV}	58.5 L h^{-1}	k_{ELGL}	0.00 h^{-1}	k_{ELSIL}	0 h^{-1}
Q_{HA}	19.5 L h^{-1}	V_T	24 L	k_{ELLIL}	0 h^{-1}
Q_{HV}	78 L h^{-1}	V_{PV}	4.98 mL	$\boldsymbol{k_{ELP}}$	$\mathbf{1 \times 10^{-2}}$ $\mathbf{h^{-1}}$
C_{LH}	1.56 L h^{-1}	V_{CGIS}	9.96 mL	$\boldsymbol{V_P}$	**11 L**
t_{LIL}	32 h	V_B	0.1 L	R_{GICS}	2.5

[a] The fitting parameters are given in boldface.

evident that the predictions are in good agreement with the experimental data. Therefore, it can be concluded that (i) the novel model is a *descriptive tool* able to reproduce the pharmacokinetics of a drug orally administered in humans; (ii) the model, once the main parameters were estimated/fitted, can be a *predictive tool* to get the in vivo behavior of a pharmaceutical system of which the in vitro behavior is known.

4.3. Administration of Diltiazem in Humans. To test the predictive ability of the model, a third case history was considered. Korhonen et al.[43] prepared and administered three different kinds of tablets containing diltiazem (a benzothiazepine used in the treatment of hypertension, angina pectoris, and some types of arrhythmia). The tablets were produced to realize three different rates of drug release (fast, medium, and slow rate). The in vitro release kinetics were determined experimentally, and they are reported in Figure 5 as symbols, together with curve fittings. The tablets were administered to eight healthy volunteers, and the hemeatic concentration evolutions of diltiazem were monitored. The experimental data are reported in Figure 6 as symbols.

Once the medium-rate in vitro kinetic was fitted, the pharmacokinetic model parameters were estimated and two of them were fitted to reproduce the in vivo data. The parameter values are reported in Table 4 (boldface type, the only two parameters fitted), and the results of the model is reported in Figure 6 as a dashed line. At this point, if the model is physically realistic and if the parameter values are chosen in the right way, the model itself should be a predictive tool; that is, without any further fitting session, the model should be able to describe the in vivo hemeatic concentration evolutions which were observed after the administration of the fast and the slow-rate tablets. Therefore, the code was applied to these two cases (the in vitro kinetics were the input of the code) and the in vivo drug

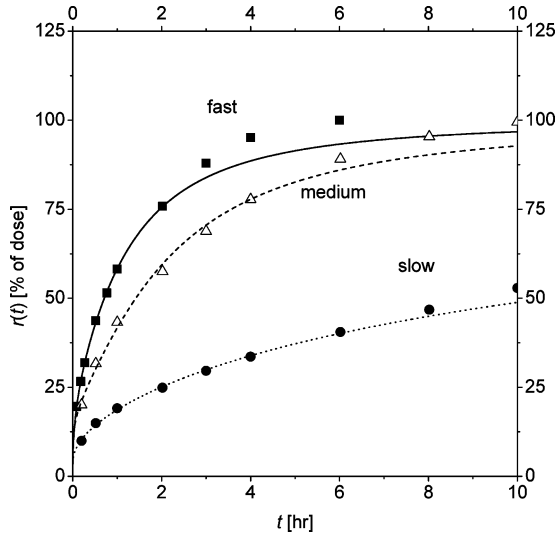

Figure 5. In vitro diltiazem release from three solid dosage forms (fast, medium, and slow release). Experimental data, symbols; curves, fitting.

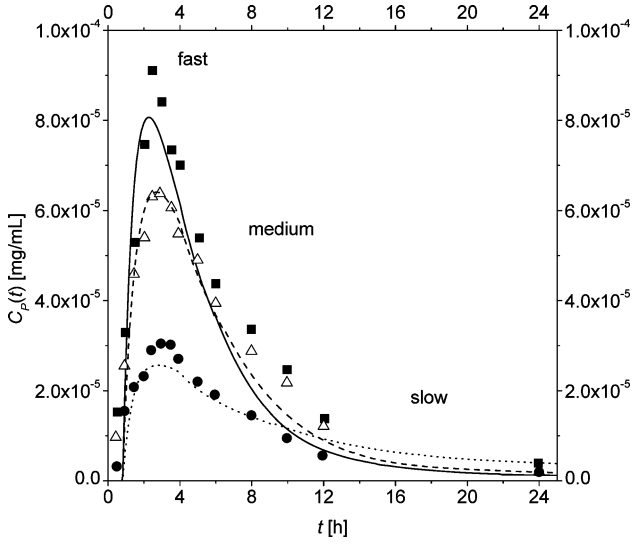

Figure 6. In vivo hemeatic diltiazem concentrations after system administrations. Experimental data, symbols; curves, model predictions.

Table 4. Parameters Values for the Simulation of the Administration of Dilitiazem in Humans[a]

t_{GL}	0.8 h	k_{AGL}	0.00 h^{-1}	β	2
t_{SIL}	3.2 h	k_{ASIL}	1.72 h^{-1}	k_{PT}	0.23 h^{-1}
V_L	1.5 L	k_{ALIL}	0.86 h^{-1}	k_{TP}	3.6×10^{-3} h^{-1}
Q_{PV}	58.5 L h^{-1}	k_{ELGL}	0.00 h^{-1}	k_{ELSIL}	0.42 h^{-1}
Q_{HA}	19.5 L h^{-1}	V_T	152 L	k_{ELLIL}	0.42 h^{-1}
Q_{HV}	78 L h^{-1}	V_{PV}	4.98 mL	$\boldsymbol{k_{ELP}}$	**0 h^{-1}**
C_{LH}	59.28 L h^{-1}	V_{CGIS}	9.96 mL	$\boldsymbol{V_P}$	**229 L**
t_{LIL}	32 h	V_B	0.1 L	R_{GICS}	6.67

[a] The fitting parameters are given in boldface.

evolution in the plasma was the output of the code (the one comparable with experimental data). The code simulations are reported in Figure 6, as a continuous line (for fast-rate tablet) and as a dotted line (for slow-rate tablet). It can be seen that the predictions are in good agreement with experimental data, the same of a level A In-Vivo/In-Vitro Correlation (IVIVC). The Level A IVIVC, however, is a purely mathematic tool, whereas the model proposed here has a much more realistic physical basis. Once more, (i) the novel model reveals itself a useful *descriptive tool* able to reproduce the pharmacokinetics of the diltiazem orally administered in humans; (ii) the model,

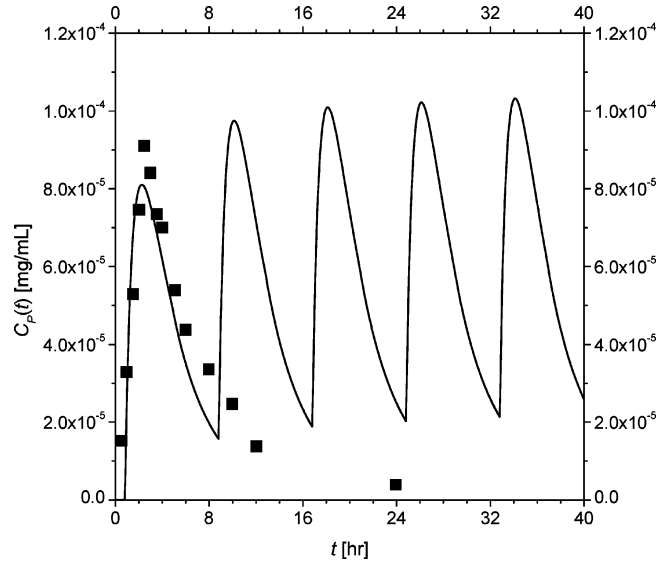

Figure 7. Predictions of the model for multiple administrations of "fast" diltiazem tablet. The experimental data (symbols) refer to a single administration.

after a simple and straightforward fitting session, became a good *predictive tool*, able to give the in vivo behavior of a new pharmaceutical system, even never tested in vivo before, on the basis of its in vitro behavior.

In the case of multiple oral administrations of tablets, the model and the calculation code has to take into account the amount of drug released by each single tablet and the positions (along the digestive system) in which the tablets are for each given time. Therefore, each tablet has to be considered in the stomach for the stomach emptying time, then in the small intestine, then in the large intestine until the emptying of the large intestine takes place. Thus, the code has to integrate the differential equations in Table 1 accounting for (i) where the tablets are and for (ii) how many tablets have been ingested and were not excreted until the given time. On the basis of such integration strategy, the multiple oral administration can be simulated as well. Table 4 reports also the emptying times for the stomach, ($t_{GL} = 0.8$ h), for the small intestine, ($t_{SIL} = 3.2$ h), and for the large intestine, ($t_{LIL} = 32$ h). Figure 7 has been obtained considering the administration of "fast" diltiazem tablets, repeated five times, each 8 h. The experimental data available (the symbols), are limited to the first administration, since the experiment from literature did not include multiple administrations. However, the code was proven able to simulate the multiple administration strategy, giving some useful information. As expected, the hemeatic peak level increases with successive administration (because some drug from the previous tablet has not been eliminated yet). The peak values increase is not unlimited, since at some point the balance between inputs and consumption/excretion will lead to a limiting value, surely larger than the peak obtained after the first administration. Of course, this behavior has to be considered in the treatment design, since the peaks after the first one could be out of the therapeutic window (i.e., the hemeatic concentration after the first administration can overcome the level over which the drug became toxic to the body).

5. Conclusions

In this work a simple but complete PBPK model was pointed out. After a review of the most accurate approaches reported in literature, a model of the animal body was built and described

by proper relationships accounting for mass balance, mass transport, and drug kinetics. The motivations for this building are to keep the number of parameters as low as possible, without an excessive lost in prediction abilities, and to have a tool able to predict the drug hemeatic levels which arise after different kind of administration(s).

The capabilities of the model were confirmed by comparison with experimental data from literature for several case histories, really different from each other: the intravenous administration of zinc sulfate in rats, the oral administration of theophylline and of diltiazem in humans. Each run confirmed the good performance of the model, keeping at minimum the number of optimizing parameters. In conclusion, the developed model was confirmed as a tool which could be of aid in performing pharmaceutical studies for novel drug release systems.

Nomenclature

$A_{GL}(t)$ = time evolution of the drug contents (masses) in the gastric lumen, kg

$A_{SIL}(t)$ = time evolution of the drug contents (masses) in the small intestine lumen, kg

$A_{LIL}(t)$ = time evolution of the drug contents (masses) in the large intestine lumen, kg

$C_{GICS}(t)$ = time evolution of the drug concentration in the gastrointestinal circulatory system, $kg \cdot m^{-3}$

$C_L(t)$ = time evolution of the drug concentration in the liver, $kg \cdot m^{-3}$

$C_P(t)$ = time evolution of the drug concentration in the plasma, $kg \cdot m^{-3}$

$C_T(t)$ = time evolution of the drug concentration in the tissues compartments, $kg \cdot m^{-3}$

$G(t)$ = time function which activates the drug release during the transit of the pharmaceutical form in the gastric lumen, unitless

$S(t)$ = time function which activates the drug release during the transit of the pharmaceutical form in the small intestine lumen, unitless

$L(t)$ = time function which activates the drug release during the transit of the pharmaceutical form in the large intestine lumen, unitless

$r(t)$ = time evolution of the in vitro measured drug release, kg

$J_{GL}(t)$ = time evolution of the mass flow rate of the drug exchanged between the gastric lumen and the gastrointestinal circulatory system, $kg \cdot s^{-1}$

$J_{SIL}(t)$ = time evolution of the mass flow rate of the drug exchanged between the small intestine lumen and the gastrointestinal circulatory system, $kg \cdot s^{-1}$

$J_{LIL}(t)$ = time evolution of the mass flow rate of the drug exchanged between the large intestine lumen and the gastrointestinal circulatory system, $kg \cdot s^{-1}$

V_B = volume of the bolus crossing the gastrointestinal tract, m^3

R_{GICS} = drug partition coefficient in the gastrointestinal circulatory system, unitless

k_{AGL} = kinetic constant of absorption from the gastric lumen, s^{-1}

k_{ASIL} = kinetic constant of absorption from the small intestine lumen, s^{-1}

k_{ALIL} = kinetic constant of absorption from the large intestine lumen, s^{-1}

k_{ELGL} = kinetic constant of elimination (metabolism and excretion), s^{-1}

k_{ELSIL} = kinetic constant of elimination (metabolism and excretion), s^{-1}

k_{ELLIL} = kinetic constant of elimination (metabolism and excretion), s^{-1}

V_{GICS} = physical volume of the gastrointestinal circulatory system, m^3

V_L = physical volume of the liver, m^3

V_P = distribution volume of the plasma compartment, m^3

V_T = distribution volume of the tissues compartment, m^3

Q_{PV} = blood volumetric flow rates of the portal vein, $m^3 \cdot s^{-1}$

Q_{HA} = blood volumetric flow rates of hepatic artery, $m^3 \cdot s^{-1}$

Q_{HV} = blood volumetric flow rates of the hepatic vein, $m^3 \cdot s^{-1}$

CL_H = hepatic clearance, $kg \cdot m^{-3}$

k_{ELP} = kinetic constant of elimination from the plasma compartment, s^{-1}

k_{PT} = mass transfer coefficient from the plasma compartment to the tissues one, s^{-1}

k_{TP} = mass transfer coefficient from the tissues compartment to the plasma one, s^{-1}

t_{GL} = residence time in the gastric lumen, s

t_{SI} = residence time in the small intestine lumen, s

t_{LIL} = residence time either in the large intestine lumen, s

k_{Ai} = kinetic constant of absorption from the ith part of the gastrointestinal lumen, s^{-1}

P_{EFFi} = effective permeability in the ith part of the gastrointestinal lumen, $m \cdot s^{-1}$

S_i = surface area of the ith part of the gastrointestinal lumen, m^2

V_i = volume of the ith part of the gastrointestinal lumen, m^3

$P_{Caco\text{-}2}$ = value of permeability in Caco-2 cells, $m \cdot s^{-1}$

R_i = the radius of the ith part of the gastrointestinal lumen, m

E_H = hepatic extraction ratio, unitless

t_{Aj} = time at which each of the potential multiple administrations begins, s

V_{PV} = volume of the portal vein, m^3

β = coefficient greater than one (which takes into account the presence, in the gastrointestinal circulatory system, of other blood vessels, besides portal vein, unitless

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