

**A new intestinal model for analysis of drug absorption and interactions
considering physiological translocation of contents**

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Abbreviations

ACAT: Advanced Compartmental Absorption and Transit, ADAM: Advanced
Dissolution, Absorption and Metabolism, AIC: Akaike's information criterion, ATOM:
Advanced translocation model, AUC: Area under the curve, BFGS:
Broyden-Fletcher-Goldfarb-Shanno, CAT: Compartmental Absorption and Transit, C_{ent} :
Drug concentration in the enterocytes, $C_{ent,u}$: Unbound drug concentration in the
enterocytes, CL: Clearance, CL_{int} : Intrinsic clearance, C_{max} : Maximum plasma
concentration, CYP: Cytochrome P450, CL_R : Renal clearance, DI: Drug interactions,
DTPA: Diethylenetriaminepentaacetic acid, D: Dispersion number, f: Free fraction, F_A :
Absorption ratio, F_G : Intestinal bioavailability, $F_A F_G$: Product of F_A and F_G , GI:
Gastrointestinal, GITA: GI-transit absorption, H_{villi} : Height of villi, iPS: Induced
pluripotent stem cells, K_i : Inhibitory constant, K_m : Michaelis constant, M: intestinal
flow rate, ME: Microvilli expansion, Napp: Numeric Analysis Program for
Pharmacokinetics, P_{app} : Apparent permeability, PBPK: Physiologically based
pharmacokinetic, P-gp: P-glycoprotein, P: Permeability, PS: Permeability surface area
product, Q: Blood flow rate, T_{ent} : Thickness of enterocyte, TLM: Translocation model,
 t_{max} : the time to reach C_{max} , V: Volume, VE: Villi expansion, V_{lum} : Volume of the
intestinal lumen, V_{max} : Maximum rate

Abstract

Precise prediction of drug absorption is key to the success of new drug development and efficacious pharmacotherapy. In this study, we developed a new absorption model, the advanced translocation model (ATOM), by extending our previous model, the translocation model. ATOM reproduces the translocation of a substance in the intestinal lumen using a partial differential equation with variable dispersion and convection terms to describe natural flow and micro-mixing within the intestine, under not only fasted but also fed conditions. In comparison with ATOM, it was suggested that a conventional absorption model, advanced compartmental absorption and transit model, tends to underestimate micro-mixing in the upper intestine, and it is difficult to adequately describe movements under the fasted and fed conditions. ATOM explains the observed nonlinear absorption of midazolam successfully, with a minimal number of scaling factors. Furthermore, ATOM considers the apical and basolateral membrane permeabilities of enterocytes separately and assumes compartmentation of the lamina propria, including blood vessels, to consider intestinal blood flow appropriately. ATOM estimates changes in the intestinal availability caused by drug interaction associated with inhibition of CYP3A and P-gp in the intestine. Additionally, ATOM can estimate the drug absorption in the fed state considering delayed intestinal drug flow. Therefore,

ATOM is a useful tool for the analysis of local pharmacokinetics in the gastrointestinal tract, especially for the estimation of nonlinear drug absorption that may involve various interactions with intestinal contents or other drugs.

Significance Statement

The advanced translocation model (ATOM) was newly developed that precisely explains various movements of intestinal contents including the fasted and fed conditions which cannot be adequately described by the current physiological pharmacokinetic models.

Introduction

Oral formulations are commonly used in pharmacotherapy because they can deliver medicinal ingredients safely in the body and can be prescribed to outpatients (Homayun et al., 2019). However, drug absorption is seriously affected by many factors, such as disintegration of the formulation, the solubility and stability of the drug, ~~or~~ interactions with intestinal contents, active efflux by transporters, such as P-glycoprotein (P-gp) and metabolism by cytochrome P450 (CYP) 3A (Mayer et al., 1996; Lu et al., 2017). For analysis of intestinal drug absorption, various pharmacokinetic models, such as Compartmental Absorption and Transit (CAT) model (Yu and Amidon, 1999), Advanced Compartmental Absorption and Transit (ACAT) model (Agoram et al., 2001; Huang et al., 2009), Advanced Dissolution, Absorption, and Metabolism (ADAM) model (Jamei et al., 2009), segregated-flow model (Cong et al., 2000; Pang and Chow, 2012), Q_{Gut} model (Gertz et al., 2010), GI-transit absorption (GITA) model (Kimura and Higaki, 2002; Haruta et al., 2002), and translocation model (TLM) (Ando et al., 2015) have been reported. Of these, Q_{Gut} model is a simple model using the parameter Q_{Gut} and has provided adequate predictions of observed intestinal availability (F_G) values (Gertz et al., 2010); however, its application to nonlinear absorption has yet to be reported. Conversely, more advanced models, such as CAT,

ACAT or ADAM, explain the heterogeneity of the gastrointestinal tracts using multiple compartments. Each compartment possesses metabolism and transport clearances, enabling reasonable simulation of time- and location-dependent drug absorption. These models have succeeded in predicting gastrointestinal drug absorption, including non-linear pharmacokinetics (Takano et al., 2016; Bolger et al., 2009).

It is noteworthy that, for these sophisticated models, multiple scaling factors are required to fill the gaps between *in vitro* and *in vivo* data. For example, scaling factors such as for the absorption surface area in each intestinal site (Hendriksen et al., 2003), V_{\max} and K_m of metabolic enzymes or transporters are applied to predictions (Takano et al., 2016). However, the function of the scaling factors would deviate from the concept of a physiologically based pharmacokinetic (PBPK) model when the movement of the drug to each section of the small intestine is not consistent with assumptions of the model.

This problem may lie with the structures of these models that explain the translocation of a drug in the lumen from upstream to downstream. Since translocation of a drug is explained via successive first-order kinetics in CAT, ACAT and ADAM, the degree of mixing is always increasing; thus, mixing tends to be underestimated upstream and overestimated downstream, leading to overestimation of drug

concentrations upstream. For substrate drugs of metabolic enzymes or transporters, drug concentrations need to be estimated accurately at each intestinal site to consider potential nonlinear pharmacokinetics. In addition, it is necessary to include the appropriate description of blood flow in the capillary in these models. To overcome this issue, the segregated-flow model has been proposed to consider divisions of blood flow into the mucosa and submucosa (Cong et al., 2000; Pang and Chow, 2012).

Previously, we developed a TLM to solve these problems (Ando et al., 2015). To minimize the calculation load, the TLM has only one compartment for absorption, but its properties of movement are time-dependent and arbitrary. However, it is theoretically difficult to accommodate for interactions with other drugs or various contents in the gastrointestinal tract. Therefore, in this study, we constructed an advanced translocation model (ATOM) that describes drug movements in the lumen by dispersion and convection terms while maintaining the features of TLM. Dispersion models based on partial differential equations have been used in the field of local pharmacokinetics to explain drug clearances (Roberts and Rowland, 1986) and extended to non-linear pharmacokinetics (Hisaka and Sugiyama, 1998). Hence, we analyzed drug movements in the gastrointestinal tract using a dispersion model in ATOM, and compared the results with those of CAT model.

Method

Construction of ATOM

The structure of ATOM and descriptions of the parameters are shown in Fig. 1 and Table 1, respectively. The source codes of ATOM used for the analysis were attached in the Supplemental text. The esophagus, stomach, caecum/colon, and portal vein were expressed as separate compartments. The intestinal lumen was expressed as one-dimensional dispersion model with a location-dependent dispersion number and time-dependent convection term. The movements of drugs, water, and intestinal contents were assumed to be the same in the lumen and thus substance independent since micro-mixing and convection occur due to intestinal motility. In addition to these tissues responsible for drug absorption, compartments for the portal vein and liver as well as central and peripheral blood pools for the whole body were assumed to simulate drug plasma concentration. Detailed physiological parameters, such as pH, P-gp and CYP3A expressions along intestine, and differential equations for tissues other than the small intestine are shown in the Supplemental text. Overall, the definition of ATOM is quite similar to TLM (Ando et al., 2015), other than the movements of intestinal contents, to achieve equivalent predictions of oral availability in the absence of

interaction. Partial differential equations related to luminal drug movements are shown in equations 1 and 2.

$$\frac{\partial C_{lum,z}}{\partial t} = D_z \frac{\partial^2 C_{lum,z}}{\partial z^2} - M_t \frac{\partial C_{lum,z}}{\partial z} - PS_{a,in,z} \frac{f_{lum} C_{lum,z}}{X_{water,z} + V_{lum,z}} + PS_{a,out,z} \frac{f_{ent} C_{ent,z}}{V_{lum,z}} \quad (z = (0,1)) \quad (1)$$

Boundary condition:

$$C_{lum,z} - \frac{D_z \partial C_{lum,z}}{M_t \partial z} = \frac{k_{sto} C_{sto} V_{sto} \partial t}{V_{lum,z}} \quad (z = 0)$$

$$\frac{\partial C_{lum,z}}{\partial z} = 0 \quad (z = 1) \quad (2)$$

In these equations, length is expressed as a ratio of volume until the location to the full volume of the intestinal lumen (V_{lum}). $C_{lum,z}$ and $C_{ent,z}$ are drug concentrations in the lumen and enterocytes at location z (i.e., within a small interval around z , the same will be applied hereafter), respectively. D_z and M_t represent the dispersion constant at location z and flow rate in the lumen at time t , respectively. The units of D_z and M_t are T^{-1} , as the length is normalized in equation 1. The metrics $V_{lum,z}$ and $X_{water,z}$ represent the volume of the physical lumen and amount of inflating water (that may be drunk,

secreted, and absorbed) at location z , respectively. The effective volume in the lumen used for calculation of the drug concentration to know absorption is $V_{lum,z} + X_{water,z}$, but it was assumed that $X_{water,z}$ does not affect the micro-mixing and flow rate. The amount of inflating water in the gastrointestinal tract was simulated with a distinct partial differential equation by considering the water secretion and absorption rate constants calculated using intestinal water content after drinking 240 mL of water (Mudie et al., 2014). The simulation results of the water profile in the stomach and small intestine and the optimized parameter values are shown in Supplemental Fig. 1 and Table S1. $PS_{a,in,z}$ and $PS_{a,out,z}$ are the permeability clearance of the uptake from the lumen to the enterocytes and of the efflux from enterocytes to the lumen, respectively, via the apical membrane at location z . In this study, $PS_{a,out,z}$ is the sum of permeability clearance ($PS_{abs,api}$) and transport clearance by P-gp ($PS_{a,Pgp}$) shown in the Supplemental text. f_{lum} and f_{ent} represent drug unbound fractions in the lumen and enterocytes, respectively. In this study, f_{lum} and f_{ent} were assumed to be 1 and same as the unbound fraction in the blood (f_b) as described in Supplemental text, respectively. $V_{ent,z}$ is the volume of the enterocytes at location z .

Dispersion number and flow rate have been constant in general dispersion models for the analysis of local pharmacokinetics; however, drug distribution in the

small intestine is quite complicated because of its structural or regional differences in motility (Sokolis, 2012). Therefore, the location-dependent dispersion number (D_z) and time-dependent flow rate (M_t) were examined in this study. They were independently optimized using the observed intestinal distribution of a non-absorptive drug, ^{99m}Tc -diethylenetriaminepentaacetic acid (^{99m}Tc -DTPA) (Haruta et al., 2002) by nonlinear least-squares method. Equations 3 and 4 were used for the calculation of D_z and M_t in both fasted and fed states.

$$D_z = A \exp(-B z) + 0.005 \quad (3)$$

$$M_t = C \left(1 - D \exp\left(\frac{|t-t_{\text{lag}}|^F}{2E^F}\right) \right) \quad (4)$$

where A, B, C, D, E, and F are the adjusting constants, t is the time after administration, and t_{lag} is the time at the minimum flow rate. Parameters A-E and t_{lag} were optimized simultaneously using the observed ^{99m}Tc -DTPA distribution in the lumen reported by Haruta et al. (2002). The parameter F was fixed to 4 in this study. Among models that fixed for both D_z and M_t , variable D_z but fixed M_t , and variable D_z and M_t , the best model was selected based on the Akaike's information criterion (AIC) value.

Regarding perpetrators of DI, drug concentrations of the perpetrator in tissues were simulated with partial differential equations in the intestine (equations 1-4) and differential equations in other tissues (shown in Supplemental text) as well as substrates. Intestinal clearance changes of P-gp transport and CYP3A metabolism upon administration of a perpetrator were calculated using equations 5 and 6 with unbound drug concentration of a perpetrator and inhibition constant for P-gp ($K_{i,Pgp}$) and CYP3A ($K_{i,CYP3A}$).

$$PS_{a,Pgp,z}^* = \frac{PS_{a,Pgp,z}}{1 + \frac{f_{ent,I_{ent,z}}}{K_{i,Pgp}}} \quad (5)$$

$$CL_{ent,z}^* = \frac{CL_{ent,z}}{1 + \frac{f_{ent,I_{ent,z}}}{K_{i,CYP3A}}} \quad (6)$$

where $PS_{a,Pgp,z}$ and $CL_{ent,z}$ represent active transport clearance of a substrate by P-gp and intestinal intrinsic clearance of a substrate by CYP3A, respectively, in the absence of a perpetrator (shown in Supplemental text). $PS_{a,Pgp,z}^*$ and $CL_{ent,z}^*$ represent $PS_{a,Pgp,z}$ and $CL_{ent,z}$ values in the presence of a perpetrator, respectively. $f_{ent,I}$ and $I_{ent,z}$ are the unbound fraction and concentration in the enterocytes of a perpetrator, respectively.

Analysis with CAT model

For comparison, CAT model with six intestinal compartments was constructed in this study (Fig. 1). The initial three compartments were for the upper intestine and the latter for the lower intestine. Transit times of the CAT model were optimized to fit the reported movements of $^{99m}\text{Tc-DTPA}$ in the lumen (Haruta et al., 2002); original and optimized transit times are shown in Supplemental Table S3. The length of the small intestine, radius of the inlet and outlet of the intestine, CYP3A and P-gp expression profile, and pH gradient were the same as those adopted in ATOM.

Simulation of drug concentrations in enterocytes and absorption to portal vein

Drug concentration in enterocytes and accumulation of the compound in the portal vein were simulated using ATOM and CAT after oral administration ($t = 0$ hr). To predict drug concentrations in enterocytes, three timepoints ($t = 0.5, 2,$ and 6 hr) were selected to evaluate the drug concentrations and compare the two models. In this analysis, a compound with low permeability (non-CYP3A and -P-gp substrate) was selected to clearly understand the difference in absorption sites between the two models. The model compound has the same physiological and pharmacokinetic parameters as midazolam (molecular weight, pKa values, $K_{m,CYP3A}$, and unbound fraction), except for

the apparent permeability in Caco-2 cells ($P_{app,Caco-2}$) and $V_{max,CYP3A}$ that were set to 0.002 cm/h (approximately 1/50 compared with midazolam) and 0 μ g/h pmol CYP3A, respectively. Regarding dispersion number and flow rate, optimized values using ^{99m}Tc -DTPA distribution of one subject (subject A) in the fasted state (shown in Fig. 2A and Supplemental Table S2) were used. Dose was set to 1 ng.

Prediction of non-linear absorption of midazolam and unbound concentration in enterocytes in both fasted and fed state

Dose-dependent absorption ratio ($F_A F_G$) and concentrations in enterocytes with regard to typical CYP3A substrate (midazolam) were simulated for 4 h after oral administration using ATOM and CAT. In simulations by ATOM, $F_A F_G$ values of midazolam were predicted in the fasted and fed states with the optimized dispersion numbers and intestinal flow rates determined using the ^{99m}Tc -DTPA distribution of subject A (Haruta et al., 2002), as shown in Fig. 2. It was confirmed that intestinal absorption of midazolam was completed at 4 h after oral administration. $F_A F_G$ values were calculated using the equation 7.

$F_A F_G$:

$$F_A F_G = \frac{X_{PV,cumulative}}{Dose} \quad (7)$$

where $X_{PV,cumulative}$ represents accumulated drug amount in the portal vein.

Reported $F_A F_G$ values were obtained from previous reports (Ando et al., 2015; Bornemann et al., 1985). Pharmacokinetic parameters of midazolam and physiological parameters used in these models are shown in Supplemental Tables S4 and S5. To predict unbound drug concentration in enterocytes ($C_{ent,u}$), simulated results at 0.16 h after administration, at which maximum concentration was observed, were utilized.

Comparison of F_G predicted values between ATOM and TLM

F_G prediction by ATOM was performed using the same dataset (Supplemental Table S6) utilized in the previous report of TLM (Ando et al., 2015), and F_G values between ATOM and TLM were compared. In the simulation by ATOM, simulation results at 4 h after oral administration are shown because intestinal absorption was completed. F_G was calculated from absorption ratio (F_A) and $F_A F_G$ using the following equations (equations 8-9).

F_A :

$$F_A = 1 - \frac{X_{\text{colon}}}{\text{Dose}} \quad (8)$$

F_G :

$$F_G = \frac{F_A F_G}{1 - \frac{X_{\text{colon}}}{\text{Dose}}} \quad (9)$$

where $X_{\text{PV,cumulative}}$ represent accumulated drug amount in the portal vein. In the prediction of F_G values, optimized values using $^{99\text{m}}\text{Tc-DTPA}$ distribution of subject A in the fasted state (shown in Fig. 2A and Supplemental Table S2) were used.

Simulation of DI mediated by CYP3A and P-gp using ATOM

Regarding CYP3A-mediated DI simulation, reported plasma concentrations of midazolam with itraconazole (a typical CYP3A inhibitor) were used (Templeton et al., 2010). Briefly, 0, 50, 200, and 400 mg itraconazole were administered ($t = 0$ h) 4 h before midazolam administration, and then 2 mg midazolam was administered ($t = 4$ h). Regarding P-gp-mediated DI simulation, reported plasma concentrations of digoxin with clarithromycin (a typical P-gp inhibitor) were used (Rengelshausen et al., 2003). Briefly, 250 mg clarithromycin was administered ($t = 0$ h) twice a day. Twenty-four

hours after the first administration of clarithromycin, 0.75 mg digoxin was administered (t = 24 h). The plasma concentrations of midazolam and digoxin were simulated for 24 h after oral administration of the substrate in the presence or absence of a perpetrator according to the reports by Templeton et al. (2010) or Rengelshausen et al. (2003). DI simulation was performed using optimized values using ^{99m}Tc -DTPA distribution of subject A in the fasted state (shown in Fig. 2A and Supplemental Table S2) were used. In this simulation, only the intestinal contribution to the DI was considered, and thus, hepatic and renal inhibitions of the metabolizing enzyme or transporter were not included. The pharmacokinetic parameters of these drugs and the physiological values used in these analyses were obtained from previous reports or results using ADMET Predictor® and GastroPlus® (Simulations Plus, Inc.) shown in Supplemental Tables S4 and S5. Two pharmacokinetic parameters (f_p for digoxin and $K_{i,Pgp}$ for clarithromycin) were obtained from the printed labeling of Digoxin Elixir (Roxane Laboratories, Inc., available online:

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/021648s000_PRNTLBL.pdf

) and the pharmacology reviews of PRADAXA (dabigatran etexilate mesylate)

Capsules (Boehringer Ingelheim Pharmaceuticals, Inc., Available online:

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022512Orig1s000PharmR_

Corrected%203.11.2011.pdf), respectively. Body weight was assumed to be 70 kg for calculating pharmacokinetics parameters.

Simulation of plasma concentration after oral administration of midazolam and digoxin in the fasted and fed state

Plasma concentration of midazolam and digoxin in the fasted and fed state were simulated for 24 h after oral administration. Dose was set to 2 mg (midazolam) and 0.75 mg (digoxin), respectively. In these simulations, the dispersion constant and flow rate in the intestine obtained using ^{99m}Tc -DTPA distribution of subject A in fasted and fed state were used. The pharmacokinetic parameters of these drugs and the physiological values used in these analyses were obtained from previous reports or results using ADMET Predictor® and GastroPlus® (Simulations Plus, Inc.) shown in Supplemental Tables S4 and S5. Body weight was assumed to be 70 kg for calculating pharmacokinetics parameters.

Calculation of dispersion model

The model with three nonlinear partial differential schemes (substrate, perpetrator, and inflating water) was solved by FDM (Hisaka and Sugiyama, 1998),

with differential schemes for the associated organs (esophagus, stomach, colon, portal vein, liver, central and peripheral compartments of the body). The number of segments was determined to be 40 considering the precision of the calculation. The Danckwerts' (closed) boundary conditions were implemented. Schemes for all the segments and compartments were calculated simultaneously with the Runge-Kutta-Fehlberg method using Numeric Analysis Program for Pharmacokinetics, Napp (version 2.31) (Hisaka and Sugiyama, 1998). The parameter fitting was performed mainly by the quasi-Newton method with the Broyden-Fletcher-Goldfarb-Shanno (BFGS) scheme implemented in Napp.

Results

Determination of dispersion number in ATOM and application to the simulation of ^{99m}Tc -DTPA distribution in the lumen considering effect of food

ATOM explains movements of intestinal contents, including the target drug, by the dispersion model with potentially variable dispersion number and flow rate. Thus, these terms need to be determined to reproduce the observed movements of intestinal contents. In the fasted state, non-absorbable ^{99m}Tc -DTPA filled the upper jejunum within 2 h after dosing, and thereafter rapidly moved to the lower jejunum, where it was retained for the next 2 h according to the report by Haruta et al. (2002) (Fig. 2A, C, E, G). In the fed state, in addition to delayed gastric emptying, movement of the contents slowed and a part of it was retained in the upper jejunum even 3 h after dosing (Fig. 2B, D, F, H). The model with a location-dependent variable dispersion number successfully reproduced the movements of the rapid passage through the upper jejunum and the subsequent retention in the lower jejunum, but only for one of the two fasted subjects (Fig. 2A and 3A). The model with a fixed dispersion term failed to reproduce the movement even for this subject (Supplemental Fig. 2). For the remaining observations, including in the fed state, a model with time-dependent flow rate, in addition to the

location-dependent dispersion number, was necessary to explain the observed movements of radioactivity in the intestine (Fig. 2B, 2D and Fig. 3).

Simulated luminal distribution of ^{99m}Tc -DTPA by CAT model

The CAT model explains movements of intestinal contents with a set of transit times from one compartment to the next. A model with reported transit times (Heikkinen et al., 2012) failed to reproduce the observed movements of ^{99m}Tc -DTPA (Supplemental Fig. 3). Radioactivity was overestimated in the upper jejunum and underestimated in the lower jejunum in this model. Therefore, appropriate values of transit time were explored through a fitting analysis. Nevertheless, the distribution of ^{99m}Tc -DTPA was not reproduced in the CAT model, especially for within the lower jejunum and ileum in both fasted and fed states (Fig. 2E, F, G, H). The radioactivity flowed out to the large intestine early within 2 h, in all simulations using CAT.

Typical difference of estimated absorption site in ATOM and CAT model

Drug distribution in enterocytes is strongly affected by differences in concentrations in the lumen because a drug moves rapidly from the lumen to enterocytes. Therefore, we compared simulated drug concentrations in the enterocytes

using ATOM (using variable D_z and fixed M_l) and CAT (Fig. 4), in which parameters were optimized to explain the observed intestinal movements of ^{99m}Tc -DTPA. In this simulation, a drug with a low permeability (approximately 1/50 compared with midazolam) was used to explain a typical difference between the two models because notable differences in drug absorption between the two models are not observed for highly permeable drugs that are absorbed rapidly from the upper jejunum. The CAT model predicted higher drug concentrations in the upper jejunum at 0.5 and 2 h, but the drug was already considerably transferred from the lower jejunum to the ileum at 6 h. In contrast, ATOM predicted that the drug began to move to the lower jejunum even at 0.5 h and was retained there for 6 h. The cumulative drug amount reaching the portal vein from each section of the intestine was calculated for these conditions (Fig. 5). These results indicated that most of the drug was absorbed in the upper jejunum in the CAT model, while the absorption occurred mainly in the lower jejunum in ATOM.

Predicting non-linear absorption ratio of midazolam and confirmation of difference in CYP3A saturation in enterocytes between ATOM and CAT model

Intestinal metabolizing enzymes and transporters are saturated when drug concentrations are higher than the Michaelis constant (K_m) in the enterocytes during the

absorption process. Therefore, nonlinear dose responses of midazolam $F_A F_G$ were simulated using the ATOM and CAT model in order to examine how drug movements in the intestinal lumen may affect oral bioavailability. When simulating results in the fasted state, $F_A F_G$ after a midazolam dose of 0.1 mg were estimated as very similar in both the ATOM and CAT model. The value increased slightly at 1 mg in the CAT model; however, it remained consistent in ATOM (Fig. 6A). At 10 mg, the difference between the $F_A F_G$ values estimated by the two models was most evident; the observed dose-response of $F_A F_G$ for midazolam was more similar to the estimation by ATOM than that of the CAT model. Estimated unbound drug concentrations in the enterocytes at 0.16 h after dosing with 10 mg were compared between the ATOM and CAT model (Fig. 6B). In the CAT model, a higher peak unbound concentration was estimated (14.36 $\mu\text{g/mL}$) compared to that in ATOM (4.53 $\mu\text{g/mL}$). Therefore, the absorption window would be narrower in CAT than in ATOM. Since $K_{m,CYP3A,u}$ for midazolam is 1.08 $\mu\text{g/mL}$ (Ando et al., 2015), the degree of saturation would be considerably more extensive in CAT than in ATOM. Additionally, $F_A F_G$ values of midazolam were estimated to be lower in the fed state than in the fasted state by ATOM (Fig. 6A) because of the lower unbound concentration in the enterocytes in the fed state (Fig. 6B).

These results suggest that weaker and more realistic non-linear pharmacokinetics of drugs may be estimated by ATOM compared with CAT.

Consistency of F_G values predicted by ATOM and TLM

ATOM is an extended model of TLM that maintains various assumptions based on intestinal structures and absorption processes. A previous report by Ando et al. (2015) showed adequate correlation between predicted and calculated F_G values. Therefore, the F_G values predicted using ATOM and TLM were compared to confirm the consistency of the two models. As a result, F_G values predicted using ATOM were within 10% of those predicted using TLM (Fig. 7) for all the drugs examined (Supplemental Table S6). Hence, the results showed the consistency of ATOM and TLM.

Simulation of CYP3A or P-gp-mediated DIs using ATOM

ATOM is an expanded model from TLM, but TLM cannot simulate location-dependent DIs because it considers only one absorption site. Clinically, since CYP3A and P-gp are greatly involved in gastrointestinal absorption and many associated clinical DIs have been reported (Galetin et al., 2010; Kharasch et al., 2004;

Chu et al., 2018), it is important to be able to accurately predict DIs caused by them. Therefore, we selected midazolam as a typical substrate of CYP3A and digoxin as a typical substrate of P-gp, and we confirmed whether ATOM could explain DIs in combination with the typical perpetrators of CYP3A and P-gp, itraconazole and clarithromycin. The simulated profiles of the inhibitors were shown in Supplemental Fig. 6. Overall, increases in the plasma concentrations of midazolam and digoxin were simulated using ATOM when perpetrators were administered considering only the intestinal contribution (Fig. 8). However, the increase in midazolam concentrations tended to be overestimated for the 50 mg dose of itraconazole even though the contribution of the liver was not considered. On the other hand, in the higher doses, the elimination phase of midazolam was somewhat underestimated probably due to ignoring the hepatic contribution. Increases in F_A values of digoxin or F_G values of midazolam were estimated as 1.25 or 2.15-2.58 -fold, respectively (Supplemental Table S8).

Difference of pharmacokinetics of midazolam and digoxin in the fasted and fed states

It was considered that the drug behavior in the small intestine was different between the fasted and fed states from the analysis in Fig. 2. Therefore, using the

dispersion number and flow rate obtained in the analysis, the differences in plasma concentrations of midazolam or digoxin were compared between the fasted and fed states and evaluated their significance. As a result, both substrates exhibited decreased C_{\max} and delayed t_{\max} in the fed state (Fig. 9), showing tendencies consistent with the previous reports on the food effects on pharmacokinetics of midazolam and digoxin (Bornemann et al., 1986, Sanchez et al., 1973).

Discussion

Precise estimation of drug concentration in the enterocytes is indispensable to consider nonlinear drug absorption and DIs in which intestinal CYP3A and P-gp are involved. Accordingly, precise consideration of drug translocation in the intestinal lumen is necessary because the concentration in the lumen directly affects the concentration in enterocytes. Food intake affects bile secretion, pH, blood flow, and drug translocation in the intestine (Jantratid et al., 2008; Kawai et al., 2011; Fleisher et al., 1999) and often seriously modifies drug absorption with changes in its solubility in the lumen. Haruta et al. (2002) observed changes in drug translocation by monitoring the radioactivity of ^{99m}Tc -DTPA under the fasted and fed conditions. However, there have been few reports of absorption models to examine the precise drug translocation.

ATOM succeeded in reproducing the distribution of ^{99m}Tc -DTPA by applying a dispersion model with location-dependent dispersion number and time-dependent intestinal flow (Fig. 2 and 3). The behavior of drugs in the small intestine is quite complex because of its structure and varied motility (Sokolis, 2012). In fact, luminal ^{99m}Tc -DTPA movement was not simulated in models with fixed dispersion numbers and intestinal flow (Supplemental Fig. S2). In a preliminary analysis, we considered a model with location-dependent dispersion number and flow, but its reproducibility of

the drug movement under fed conditions was inferior to that of the adopted model.

Therefore, time-dependent intestinal flow was also necessary to explain complex drug translocations in some cases.

Previously, GITA model explains luminal drug movements precisely using a set of first-order transit rates and lag-time (Sawamoto et al., 1997; Kimura and Higaki, 2002; Haruta et al., 2002). However, GITA model lacks the location-dependent physiological changes in the intestine, whereas CAT and ADAM considers them. In this study, however, CAT model could not reproduce luminal ^{99m}Tc -DTPA distribution, regardless of optimizing luminal transit times (Fig. 2E, F, G, H and Supplemental Fig. 2). For this reason, CAT appeared to overestimate $F_A F_G$ of midazolam at lower doses, whereas ATOM predicted the observed values satisfactorily (Fig. 6A). CYP3A expression level is higher in the upper intestine (Paine et al., 1997); thus, the retention of a drug in the upper intestine would be important for intestinal metabolism. CAT estimates a stronger saturation of CYP3A because of its higher concentration in the upper intestine compared with ATOM. The present study implies that intestinal absorption models that cannot explain intestinal translocation may lead to a misunderstanding of the nonlinear dynamics of drug absorption.

Intestinal DIs involving CYP3A or P-gp occur because of high drug concentration in the intestine after oral administration (Delavenne et al., 2013; Lilja et al., 2000). This is especially applicable for weak CYP3A inhibitors, since AUC increase of them mainly depends on intestinal DIs rather than hepatic ones where drug concentrations may be lower (Yamada et al., 2020). Several CYP3A and P-gp-mediated DIs have been analyzed using PBPK models (Yamazaki et al., 2019, Heikkinen et al., 2012); however, the appropriateness of drug concentrations in the small intestine was not discussed in detail. Currently, DI guidance for the US, Europe, and Japan only document one formula for estimation of intestinal drug concentration, which divides the dose by the amount of drinking water (250 mL). This is a useful approach for risk management, but far from the concept of PBPK analysis.

In this study, the significances of DIs for midazolam and digoxin cases were explained to a large extent by the intestinal contribution (Fig. 8), suggesting importance of the intestinal DIs. The DI between midazolam and itraconazole was extensively studied and contributions by the metabolites of itraconazole have been clarified (Isoherranen et al., 2004, Prieto Garcia et al., 2018, Chen et al., 2019) whereas the intestinal contribution was not fully evaluated. In this study, the contribution by the metabolites was not considered because their concentrations in the enterocytes are

unknown and would be lower than those in the liver. Nevertheless, in this study, ATOM somewhat overestimates the intestinal interaction by itraconazole. In the future, further detailed studies of DIs are necessary to conclude the precise interactions due to the intestinal contributions.

Regarding pharmacokinetics of digoxin, the contribution of P-gp may be not only in the intestine but potentially in the liver and kidney (Yin and Wang, 2016, Liu and Sahi, 2016). Therefore, DIs in the liver and kidney should also be considered, which was not achieved in this study. Nevertheless, the analysis of Fig. 8B demonstrated the significance of the intestinal contribution. On the other hand, the predictive performances of P-gp substrates such as cyclosporin and saquinavir were insufficient (Supplemental Table S6). It may be due to relatively high doses of these drugs, and thus causing saturation of P-gp. An extensive simulation study of P-gp substrates including verapamil, fexofenadine, talinolol as well as digoxin was performed by using TLM, and it was suggested that higher doses such as 100 mg, the risk of P-gp-mediated DI would generally be reduced because of saturation of P-gp efflux (Ando et al. 2015).

In addition to the luminal translocation issue, it is necessary to consider the permeability of the basolateral membrane to precisely estimate the drug concentration in

enterocytes. In the reported absorption models, ambiguity remains in the descriptions of the basolateral permeability because only one compartment is arranged for the portal blood along with the whole length of the small intestine. If permeation across the basolateral membrane were bidirectional, a drug would be back-secreted from the blood to the lower intestine immediately after absorption begins in the upper intestine. Since no one has reported this phenomenon, it can be assumed that permeation across the basolateral membrane is not truly bidirectional, implying that blood flow limited absorption cannot be considered by these models; even though the effect of blood flow on drug absorption has been discussed (Winne, 1978, Schulz and Winne, 1987; Chen and Pang, 1997; Pang and Chow, 2012). To solve this problem, the portal blood compartment needs to be separated conceptually by the location of the intestine as achieved in TLM and ATOM. Additionally, it is necessary to evaluate the permeability of the basolateral membrane separating from that of the apical membrane to incorporate these parameters into the model. This is still a challenging issue, but by using multifunctional cell systems such as induced pluripotent stem (iPS) cells (Kabeya et al., 2020) and CYP3A4-expressed intestinal cells (Takenaka et al., 2017), it may be possible to discriminate various kinetic intracellular events using selective inhibitors or knock-down techniques.

To precisely reproduce *in vivo* situations, PBPK model is composed of complicated structures and parameters, including multiple scaling factors for filling gaps between *in vitro* and *in vivo* studies. However, in the case of the intestinal absorption model, if the scaling factor is used to adjust for ambiguity of the absorption site, it should lose its validity for drugs with different absorption sites. In other words, the role of scaling factors is to adjust simply quantitative relationships between *in vitro* and *in vivo*. Regarding CYP3A and P-gp substrates, Takano et al. (2016) reported a non-linear prediction of pharmacokinetics of midazolam successfully with a scaling factor for V_{\max} of CYP3A and explained dose-dependent $F_A F_G$. However, the appropriateness of the scaling factor was not discussed. In this study, the nonlinear absorption of midazolam was predicted using ATOM minimized to only the scaling factors of passive permeability and P-gp expression (Fig. 6A and Supplementary text). Therefore, we expect that analysis using ATOM would be a useful approach for predicting pharmacokinetics in multiple situations including drug development.

Theoretically, the predicted clearance of an organ pharmacokinetic model is determined by the residence time distribution of the solute and the clearance in the organ (Roberts et al., 1988). ATOM and TLM are designed to be equivalent for these values, so there should be no difference in prediction performance. The performances of

ATOM and TLM are comparable to other sophisticated models such as ACAT (Ando et al., 2015, Gertz et al., 2010, Yau et al., 2017). However, their superiority has not been proved yet. Currently, some *in vitro* parameters for predicting oral availability including the transport activity by P-gp (Bentz et al., 2013) are variable between experiments and reliable *in vivo* F_A and F_G values are insufficient (Hisaka et al., 2014). Therefore, further studies are necessary to select the better absorption model.

In the process of drug absorption, dissociation and dissolution are also regulating factors, especially for highly lipophilic and potentially insoluble compounds. These factors are readily influenced by luminal pH, which is lower in the stomach (pH: 1.5-5.0), but gradually increases in the intestine (pH: 5.0-7.4) (DeSesso and Williams, 2008). At present, ATOM does not include these processes and only considers drug aqueous solutions. Therefore, it is necessary to expand ATOM by incorporating these processes to broaden its applicability.

In conclusion, a newly constructed absorption model, ATOM, could simulate intestinal drug behavior using minimum scaling factors, thereby providing reasonable interpretations of change in drug absorption and of DI mediated by CYP3A and P-gp. In the future, ATOM is expected to be applied to drug development and clinical management.

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Authorship Contributions

Participated in research design: Asano, Sato, Hisaka.

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Footnotes

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Figure legends

Fig. 1 Structures of ATOM (A) and CAT model (B).

Parameter z shows the normalized length from the inlet of the small intestine, which is equal to the ratio of intestinal volume until the location to the full volume. Descriptions of parameters in these models are shown in Table 1.

Fig. 2 Simulated movements of ^{99m}Tc -DTPA in the gastrointestinal tract by ATOM (A, B, C and D) and CAT (E, F, G and H) in fasted and fed state.

The observed ^{99m}Tc -DTPA distribution in the lumen was taken from a previous study (Haruta et al., 2002), which reported its distribution in two subjects. Simulated results of ^{99m}Tc -DTPA distribution of subject A in the fasted condition (A and E), subject A in the fed condition (B and F), subject B in the fasted condition (C and G), and subject B in the fed condition (D and H). The left (A, B, C and D) and right (E, F, G and H) panels show the simulated results by ATOM and CAT, respectively. Open circles, closed circles, open squares, and open triangles represent the observed distributions in the stomach, upper intestine, lower intestine, and caecum/colon, respectively. The lines represent the simulated ^{99m}Tc -DTPA distributions in each organ. In ATOM, distributions at 40 locations were simulated, and the upper 24 segments were assigned

to the upper intestine and the other 16 segments to the lower intestine corresponding to CAT model using the index of the length from the inlet in the intestine. CAT model assumes that the small intestine is divided into six portions, as shown in Fig. 1.

Fig. 3 Optimized change of location-dispersion number (A and B) and time-dependent flow rates (C and D) in the small intestine in ATOM.

Each dispersion number and flow rate were obtained by optimization using the observed ^{99m}Tc -DTPA distribution reported by Haruta et al. (2002), as shown in Fig. 2. Solid and dotted lines represent the obtained profiles of the dispersion number or flow rate using ^{99m}Tc -DTPA distribution of subject A and subject B, respectively. Panels A and C show the obtained dispersion numbers and flow rates in the fasted condition, while panels B and D represent those in the fed condition. The equations for calculating the location-dependent dispersion number and time-dependent flow rate are shown in the Method.

Fig. 4 Demonstrative simulation using ATOM and CAT model of drug concentrations in enterocytes in the small intestine at 0.5 h (A), 2 h (B) and 6 h (C) after oral administration.

Solid and broken lines show simulated results by ATOM and CAT model with optimized transit times, respectively. The model compound has the same physiological and pharmacokinetic parameters (molecular weight, pKa values, $K_{m,CYP3A}$, and unbound fractions in plasma, blood and enterocytes) as midazolam, except for its apparent permeability in Caco-2 cells ($P_{app,Caco-2}$) and $V_{max,CYP3A}$, set as 0.002 cm/h (approximately 1/50 compared with midazolam) and 0 μ g/h pmol CYP3A, respectively. The dispersion number and flow rate in the intestine obtained in the analysis shown in Fig. 2A using ^{99m}Tc -DTPA distribution of subject A in the fasted state as reported by Haruta et al. (2002) were adapted. Dose was set to 1 ng.

Fig. 5 Demonstrative simulation of cumulative drug absorption by ATOM and CAT model.

Solid and broken lines represent cumulative drug transfer into the portal vein simulated by ATOM and CAT with optimized transit times, respectively. The simulation was performed using the same model drug, which was absorbed only by passive diffusion with low permeability, as shown in Fig. 4. The dispersion number and flow rate in the intestine obtained in the analysis shown in Fig. 2A using ^{99m}Tc -DTPA distribution of

subject A in the fasted state as reported by Haruta et al. (2002) were adapted. Dose was set to 1 ng.

Fig. 6 Simulation of dose-dependent $F_A F_G$ change of midazolam (A) and comparison of simulated unbound drug concentration in enterocytes between ATOM and CAT with optimized transit times (B) in fasted and fed state.

In panel A, closed circles represent reported $F_A F_G$ values according to previous reports (Ando et al., 2015; Bornemann et al., 1985). Black bold, black dotted, and blue bold lines represent the predicted dose-dependent $F_A F_G$ profiles of midazolam by ATOM in fasted state, by CAT in fasted state, and by ATOM in fed state, respectively.

In panel B, the maximum unbound concentration in enterocytes was reached in two models at 0.16 h after oral administration. Black bold, black dotted, and blue bold lines represent the predicted unbound concentration of midazolam in enterocytes by ATOM in fasted state, by CAT in fasted state, and by ATOM in fed state, respectively. The red line represents $K_{m,CYP3A,u}$ of midazolam (1.08 $\mu\text{g/mL}$), as reported previously (Ando et al., 2015). In this analysis, the dispersion number and flow rate in the intestine obtained in the analysis shown in Fig. 2A using $^{99\text{m}}\text{Tc}$ -DTPA distribution of subject A in the fasted state as reported by Haruta et al. (2002) were adapted.

Fig. 7 Comparison of F_G values using ATOM and TLM.

F_G values of 17 CYP3A or CYP3A/P-gp substrates (alfentanil, alprazolam, buspirone, cisapride, cyclosporin, felodipine, lovastatin, midazolam, nifedipine, nisoldipine, rifabutin, saquinavir, sildenafil, simvastatin, trazodone, triazolam, and zolpidem) were evaluated using ATOM. The dotted and solid lines represent 100 % and 90 - 110 % of the predicted F_G values obtained using TLM, respectively. F_G values predicted by TLM were obtained from a previous report by Ando et al. (2015).

Fig. 8 Demonstrative simulation of CYP3A (A) or P-gp (B) mediated-DI using ATOM.

In panel A, open circles, closed circles, open squares, and open triangles represent the concentration of midazolam in plasma with 0, 50, 200, and 400 mg itraconazole, respectively. The observed plasma concentrations of midazolam by Templeton et al. (2010) were used in the simulation. Itraconazole was administered once daily at 50, 200, or 400 mg during the study (from $t = 0$ h). Midazolam was administered 4 h after the administration of itraconazole.

In panel B, open and closed circles represent the plasma concentration of digoxin with 0 and 250 mg clarithromycin twice daily. Observed plasma concentrations of digoxin by

Rengelshausen et al. (2003) were used in the simulation. Clarithromycin was administered twice daily (250 mg each) during the study period (from $t = 0$ h). Digoxin was administered 24 h after the first administration of clarithromycin. In both analyses, the dispersion number and flow rate in the intestine obtained in the analysis shown in Fig. 2A using ^{99m}Tc -DTPA distribution of subject A in the fasted state reported by Haruta et al. (2002) were adapted. The symbols and error bars represent the mean concentration in plasma and SD, respectively.

Fig. 9 Plasma concentration of midazolam (A) and digoxin (B) after oral administration in fasted and fed state.

Solid and broken line represent the plasma concentration profile of midazolam (A) or digoxin (B) in fasted and fed state, respectively. Doses were set to 2 mg (midazolam) or 0.75 mg (digoxin). The dispersion number and flow rate in the intestine obtained in the analysis shown in Fig. 2A and 2B using ^{99m}Tc -DTPA distribution of subject A in the fasted and fed state as reported by Haruta et al. (2002) were adopted. Predicted C_{\max} values of midazolam in fasted and fed state were 0.0225 and 0.0164 $\mu\text{mol/L}$, and those of digoxin in fasted and fed state were 3.51 and 1.51 ng/mL , respectively. Predicted t_{\max}

values of midazolam in fasted and fed state were 0.86 and 1.35 h, and those of digoxin in fasted and fed state were 0.96 and 1.20 h, respectively.

Table 1 Descriptions of parameters in ATOM and CAT

Parameters	Description
CL_{ent}	intestinal metabolic clearance by CYP3A
CL_{int}	hepatic intrinsic clearance
CL_R	renal clearance
D_z	location-dependent dispersion number
f_h	hepatic unbound fraction
k_{col}	transit rate from the ileum to the caecum/colon
k_{es}	transit rate of drug from the esophagus to the stomach
k_{feces}	transit rate from the caecum/colon to the feces
k_{nl}	transit rate from the nth peripheral compartment to the central compartment
k_{sto}	transit rate of drug from the stomach to the jejunum
$k_{t,n}$	transit rate from the nth compartment in the small intestine in CAT
k_{In}	transit rate from the central compartment to the nth peripheral compartment
M_t	time-dependent intestinal flow rate

$PS_{a,in}$	permeability clearance from the lumen to the enterocytes in the apical membrane
$PS_{a,out}$	permeability clearance from the enterocytes to the lumen in the apical membrane
$PS_{b,in}$	permeability clearance from the enterocytes to the lamina propria in the basolateral membrane
$PS_{b,out}$	permeability clearance from the lamina propria to the enterocytes in the basolateral membrane
PS_{ent}	overall clearance in the basolateral membrane
Q_h	blood flow in the liver
Q_{ha}	arterial blood flow in the liver
Q_{pro}	blood flow rate in the lamina propria
Q_{pv}	blood flow rate in the portal vein

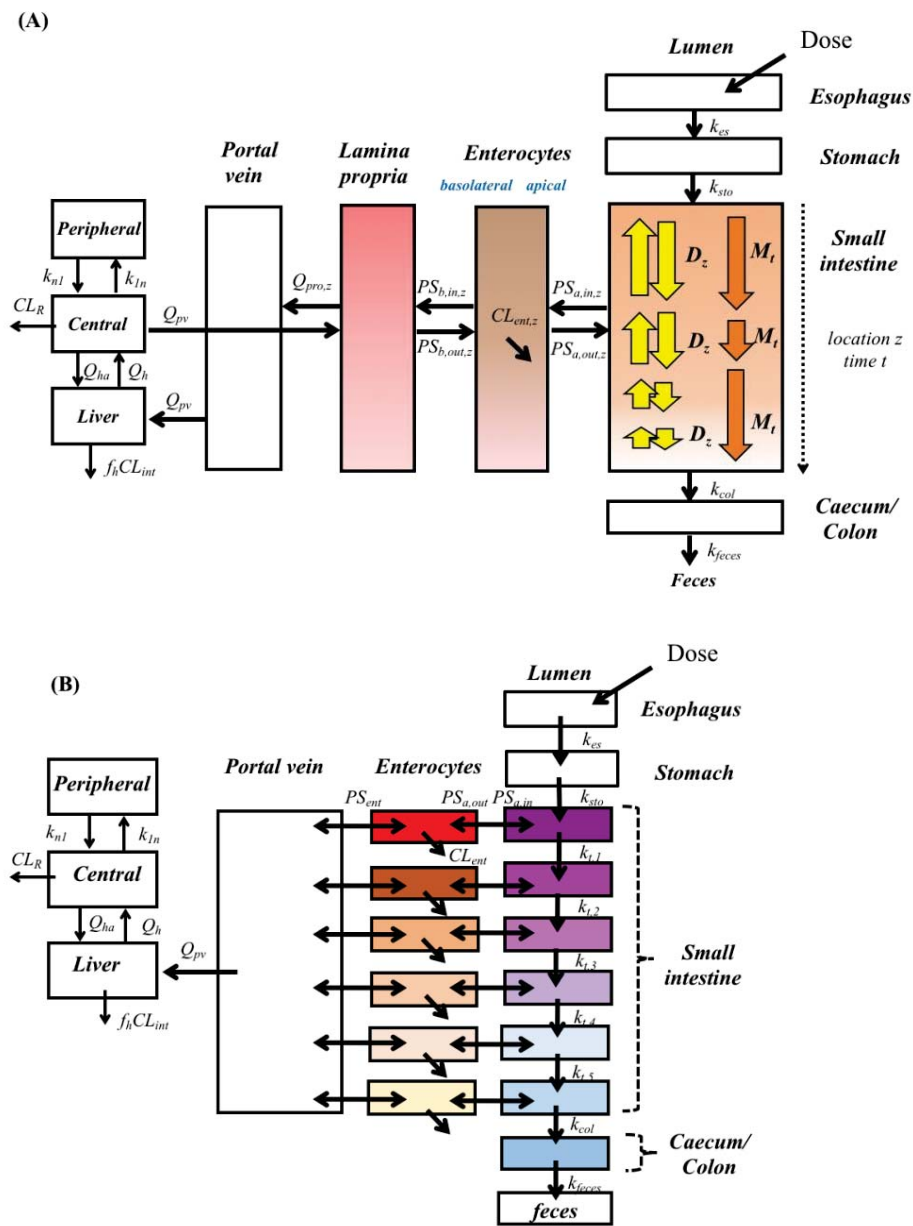


Fig. 1

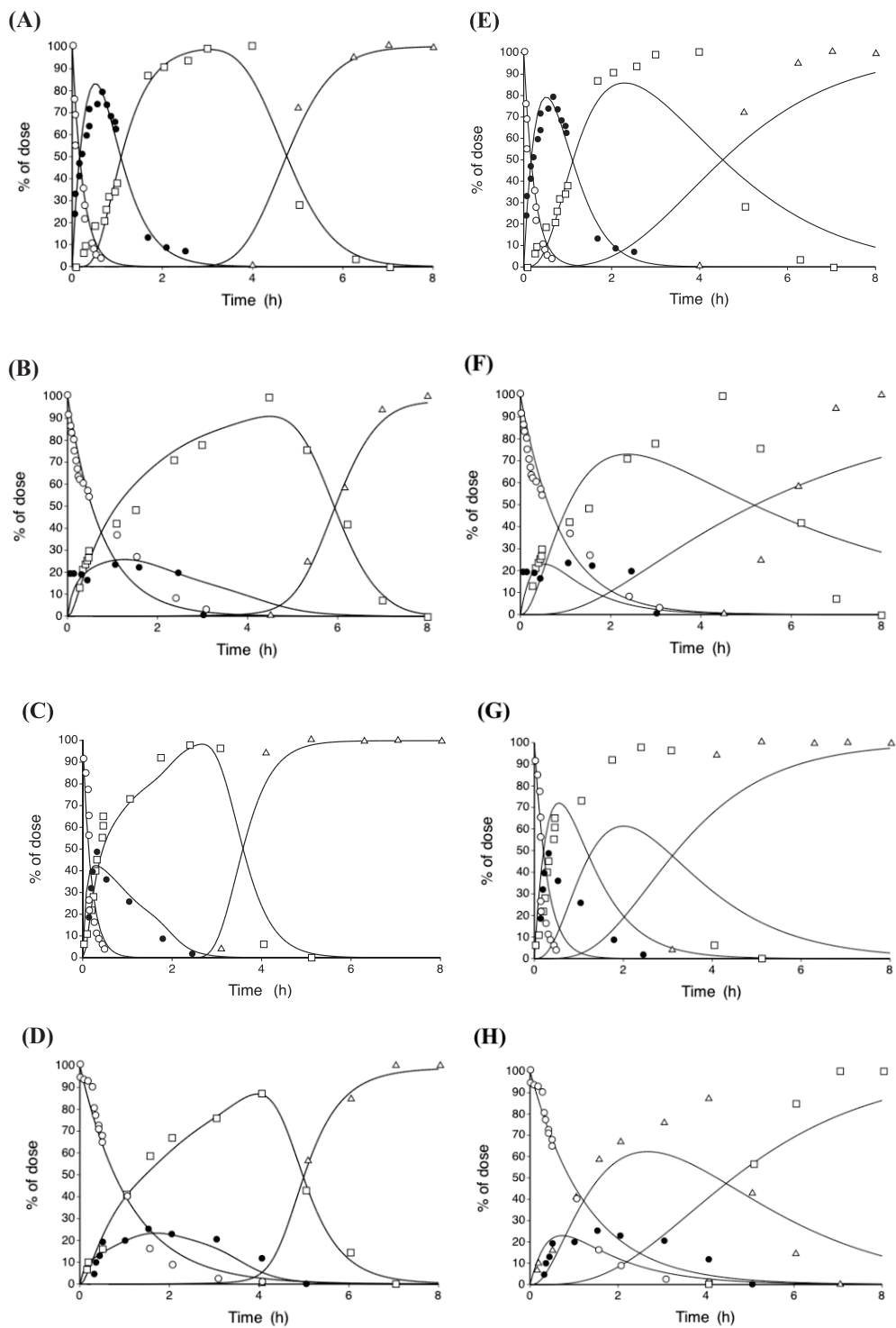


Fig. 2

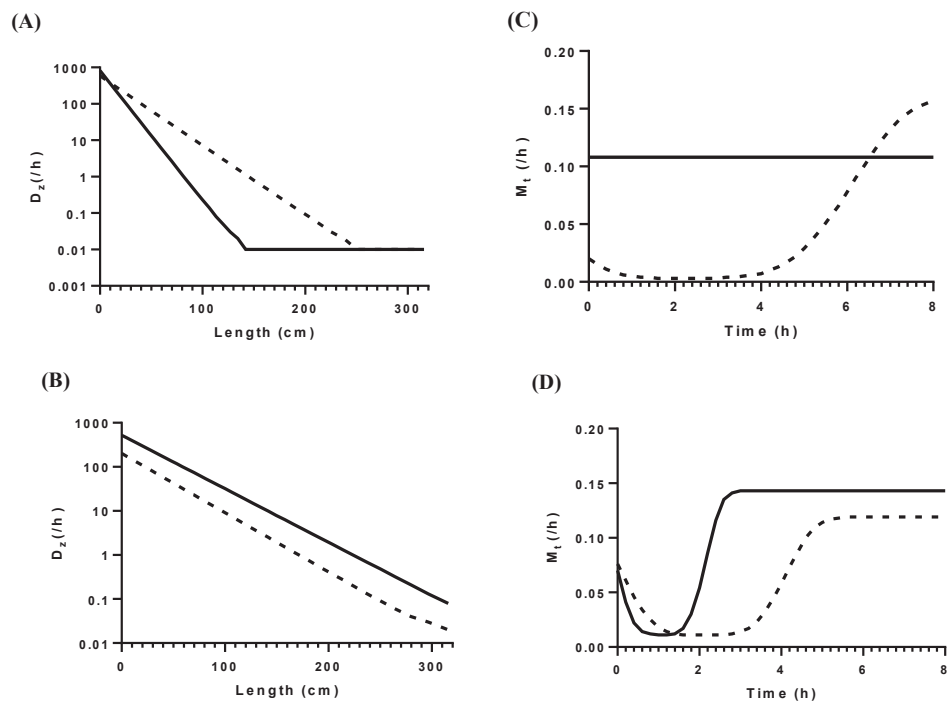


Fig. 3

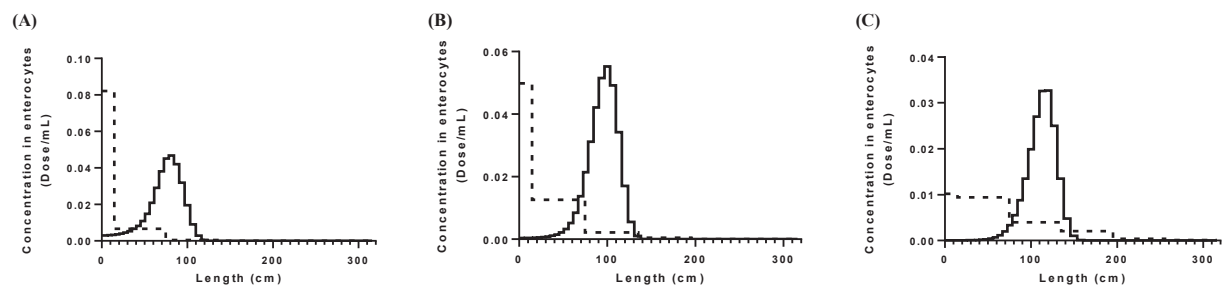


Fig. 4

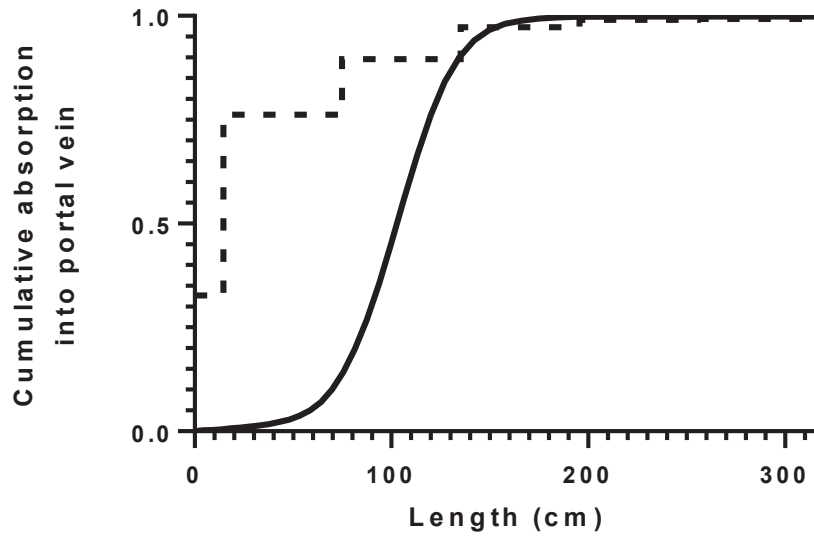


Fig. 5

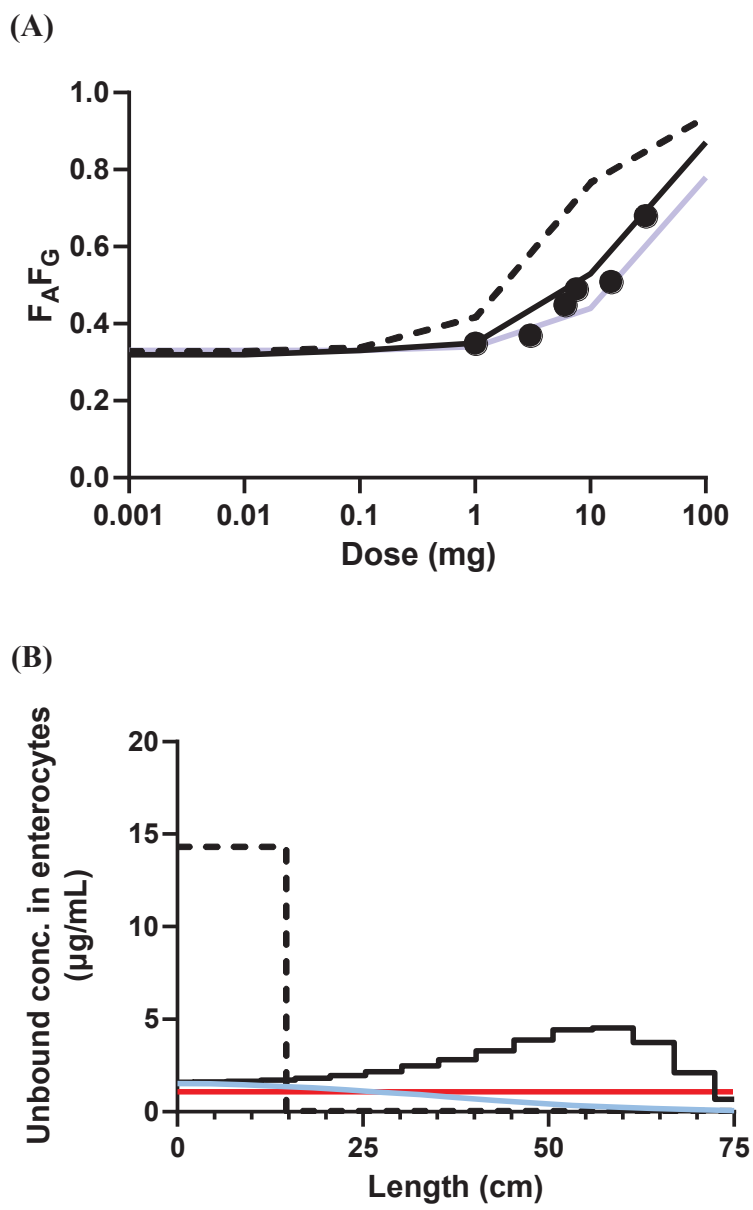


Fig. 6

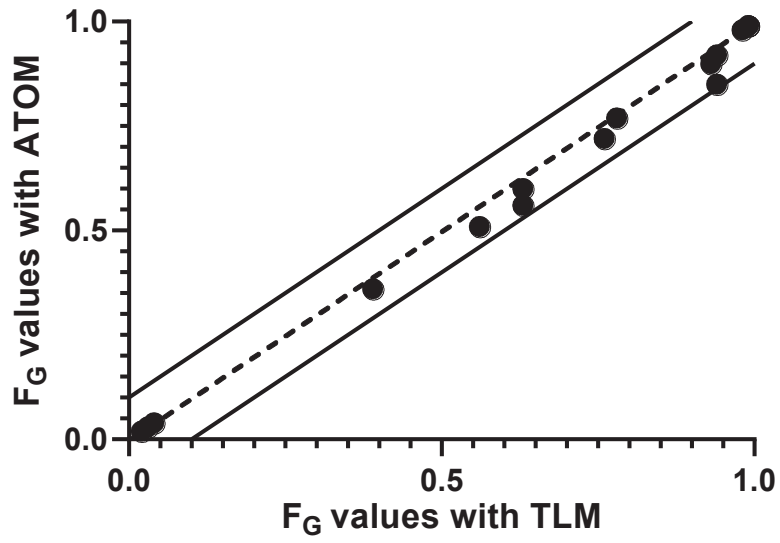


Fig. 7

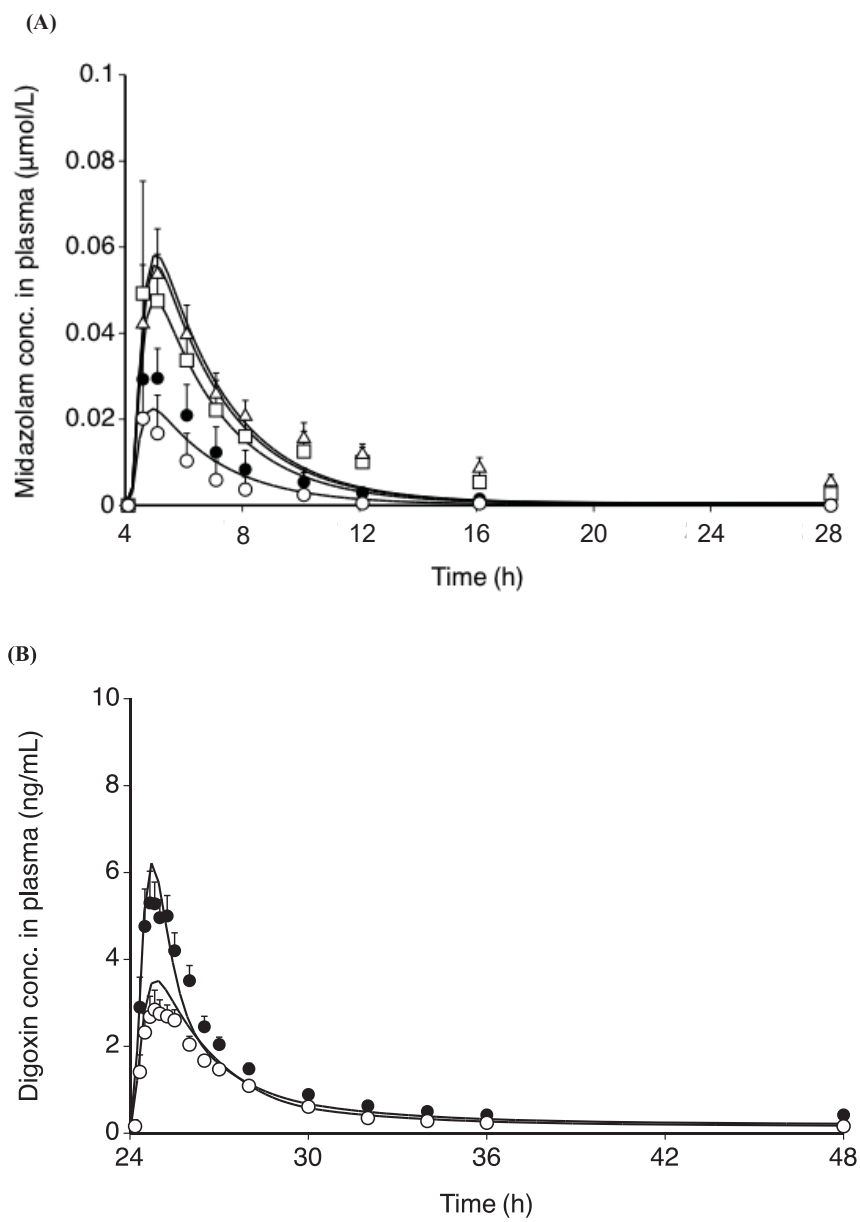


Fig. 8

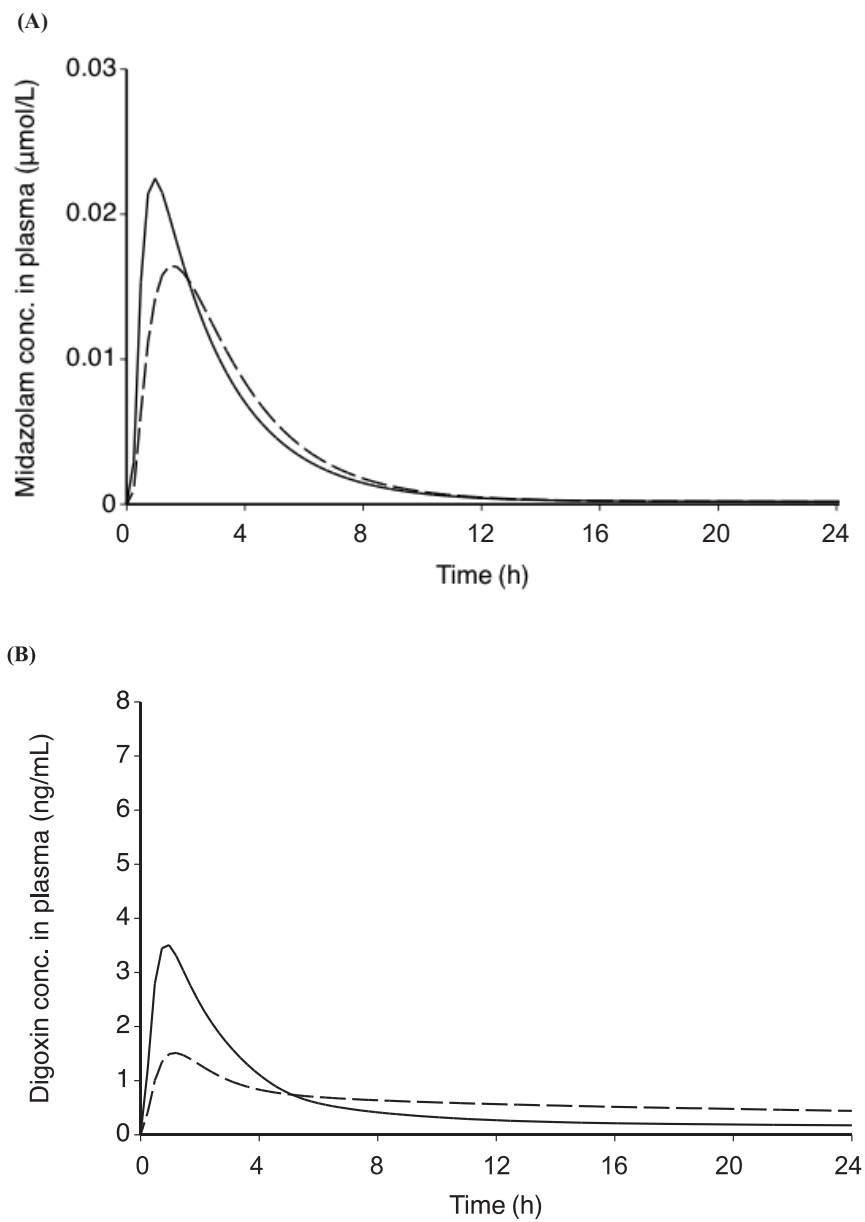


Fig. 9

Supplementary file

Article's Title;

A new intestinal model for analysis of drug absorption and interactions considering physiological translocation of contents

Authors;

Satoshi Asano, Aoi Yoshitomo, Shizuka Hozuki, Hiromi Sato, Yasuhiro Kazuki, and Akihiro Hisaka

Journal Title;

Drug Metabolism and Disposition

Supplementary text 1

Model construction in esophagus, stomach, enterocytes, lamina propria, portal vein, central and peripheral compartment

In ATOM, the concentration profiles of drugs in the tissues except for the intestine are expressed by the following differential equations S1-8.

Esophagus:

$$\frac{dC_{es}}{dt} = -k_{es}C_{es} \quad (S1)$$

Stomach:

$$\frac{dC_{sto}}{dt} = k_{es}C_{es}V_{es}/V_{sto} - k_{sto}C_{sto} \quad (S2)$$

where C_{es} , C_{sto} , k_{es} , k_{sto} , V_{es} , and V_{sto} represent drug concentrations, elimination rate constants, and volumes for the esophagus and stomach, respectively. At the initial condition, all doses and drinking water were located in the esophagus. It was assumed that the drinking water does not change the volumes in the esophagus and stomach and moves with the drug in accordance with equations S1 and S2. k_{es} and k_{sto} were used in both drugs and water simulations because their movements were assumed to be the same in the esophagus and stomach.

Enterocytes and lamina propria:

$$\frac{\partial C_{ent,z}}{\partial t} = PS_{a,in,z} \frac{f_{lum}C_{lum,z}V_{lum}}{V_{water}+V_{lum}} - (PS_{a,out,z} + CL_{ent,z} + PS_{b,out,z})f_{ent}C_{ent,z} + f_{pro}PS_{b,in,z}C_{pro,z} \quad (S3)$$

$$\frac{\partial C_{pro,z}}{\partial t} = PS_{b,in,z}f_{ent}C_{ent,z} - \left(\frac{Q_{pro,z}}{f_b} + f_{pro}PS_{b,in,z}\right)C_{pro,z} \quad (S4)$$

where $C_{pro,z}$ is the drug concentration in the lamina propria, including blood capillaries at location z . $PS_{b,in,z}$ and $PS_{b,out,z}$ are the permeability clearance of reuptake from the lamina propria to enterocytes and of efflux from enterocytes to lamina propria, respectively, via the basolateral membrane at location z . $CL_{ent,z}$ represents intestinal intrinsic clearance in enterocytes at location z . $Q_{pro,z}$ represents blood flow of the blood capillaries in the lamina propria at location z . f_{ent} and f_{pro} represent the unbound fraction of the drug in the enterocytes and lamina propria, respectively. f_{pro} was assumed to be 1. In this study, f_{ent} values were tentatively assumed to be equal to f_b . However, it does not affect the availability as shown in a sensitivity analysis of f_{ent} values on availability of midazolam in a linear condition (Supplemental Fig. 5).

Portal vein and liver:

$$V_{pv} \frac{dC_{pv}}{dt} = \sum_z \frac{Q_{pro,z}}{f_b} C_{pro,z} - Q_{pv} C_{pv} \quad (S5)$$

$$V_{liver} \frac{dC_{liver}}{dt} = R_B(Q_{pv} C_{pv} + Q_{ha} C_p) - \left(\frac{R_B(Q_{pv} + Q_{ha})}{K_{p,liver}} + f_h CL_{int} \right) C_{liver} \quad (S6)$$

where C_p , C_{pv} , V_{pv} , and Q_{pv} represent plasma concentration in systemic circulation, plasma concentration, volume, and blood flow in the portal vein, respectively. C_{liver} , V_{liver} , and Q_{ha} represent drug concentration, volume, and blood flow in the liver and blood flow in the hepatic artery, respectively. R_B , $K_{p,liver}$, f_h , and CL_{int} represent the blood/plasma partition coefficient, liver/plasma partition coefficient, unbound fraction in the liver and hepatic intrinsic clearance, respectively.

Central and peripheral compartments:

$$V_d \frac{dC_p}{dt} = \frac{R_B(Q_{pv}+Q_{ha})}{K_{p,liver}} C_{liver} + \sum_{i=1}^n k_{i1} X_{peri,i} - (R_B Q_{ha} + \sum_{i=1}^n k_{1i} + CL_R) C_p \quad (S7)$$

$$\frac{dX_{peri,i}}{dt} = k_{1i} V_d C_p - k_{i1} X_{peri,i}$$

($i = 0$ for itraconazole, $i = 1$ for midazolam and clarithromycin, $i = 2$ for digoxin) (S8).

where V_d and CL_R represent the distribution volume in the central compartment (rapid equilibrium is assumed between plasma concentration) and renal plasma clearance, respectively. For peripheral compartments, $X_{peri,i}$ is the drug amount in the i -th peripheral compartment, and k_{1i} and k_{i1} represent distribution constants from the central to peripheral compartment and peripheral to central compartment, respectively. CL_R is the sum of renal clearance mediated by P-gp ($CL_{R,Pgp}$) and that by other mechanisms ($CL_{R,nonPgp}$).

Model structure of the intestine in ATOM and CAT

CYP3A and P-gp expression levels in each location, pH changes in the lumen, surface area in enterocytes, volume of enterocytes and lamina propria, and blood flow in the lamina propria were shown using equations S9-15. The relative P-gp expression level in each location was shown because the absolute P-gp amount was not reported. Blood flow in the lamina propria (Q_{pro}) was assumed to be 18,000 mL/h, which assumes that the blood flow into the superior mesenteric artery is 37,200 mL/h accounting for 10% of the cardiac output, and 80 % of the blood flow of the superior mesenteric artery flows into the mucosa, and then 60% of the mucosal blood flows into the epithelial cells of the villi (Jamei et al., 2009)

CYP3A expression:

$$\text{Exp}_{\text{CYP3A},z} = \frac{\text{Exp}_{\text{CYP3A,whole}}}{L_{\text{si}}} \left(1 - \frac{z}{L_{\text{si}}}\right) \quad (\text{S9})$$

Relative P-gp expression:

$$\text{Exp}_{\text{Pgp},z} = \frac{\text{Exp}_{\text{Pgp,whole}}}{L_{\text{si}}} \left(\frac{z}{L_{\text{si}}}\right) \quad (\text{S10})$$

pH changes in the lumen:

$$\text{pH}_{\text{lumen},z} = 5.85 + \text{pH}_{\text{grad}} \frac{z}{L_{\text{si}}} \quad (\text{S11})$$

Surface area in enterocytes:

$$S_{\text{ent},z} = \pi(r_{\text{in}} + r_z) \sqrt{(r_{\text{in}} - r_z)^2 + L_z^2} \text{ PE VE} \quad (\text{S12})$$

Volume of enterocytes:

$$V_{\text{ent},z} = S_{\text{ent},z} T_{\text{ent}} \quad (\text{S13})$$

Volume of lamina propria:

$$V_{\text{lam},z} = \frac{S_{\text{ent}} H_{\text{villi}}}{\text{VE}} - V_{\text{ent},z} \quad (\text{S14})$$

Blood flow in lamina propria:

$$Q_{\text{pro},z} = Q_{\text{pro}} \frac{S_{\text{ent},z}}{S_{\text{ent,whole}}} \quad (\text{S15})$$

where L_{si} , $\text{Exp}_{\text{CYP3A,whole}}$, $\text{Exp}_{\text{Pgp,whole}}$, and r_{in} represent the total normalized length of the intestine ($L_{\text{si}} = 1$), the total expression level of CYP3A and P-gp in the intestine, and radius in the inlet of the small intestine, respectively. z is within the range of 0 and L_{si} ($0 \leq z \leq L_{\text{si}} = 1$).

PE, VE, H_{villi}, S_{ent,whole}, T_{ent}, and ME represent plicate expansion, villi expansion, height of villi, total surface area of enterocytes, height of enterocytes, and microvilli expansion, respectively. The absolute expression level of P-gp has not been clearly reported; therefore, it was expressed as a relative expression level and the whole expression level was set to 1. The values of these parameters were obtained from the previous report by Ando et al. (2015).

Membrane permeability model between *in vitro* and *in vivo*

Equations S16-19 were used to calculate *in vivo* permeability coefficients from *in vitro* permeability using the concept shown in Supplemental Fig. 4, which was same with TLM (Ando et al., 2015). Apparent permeability in Caco-2 cells (P_{app,Caco-2}) was transferred into the permeability of a single membrane (P_{s,Caco-2}) using equation S16 from the previous report by Gertz et al. (2010).

$$P_{s,Caco-2} = \frac{1+ME_{Caco-2}}{ME_{Caco-2}} P_{app,Caco-2} \quad (S16)$$

where ME_{Caco-2} represents the surface area ratio in apical and basolateral membranes in Caco-2 cells and was set as 4 based on a previous report by Ohura et al. (2011).

Then, *in vivo* membrane permeability (P_{in vivo}) was calculated from P_{s,Caco-2} using equation S17.

$$P_{in\ vivo} = P_{s,Caco-2} \text{ psf}_{passive} \quad (S17)$$

where psf_{passive} represents a scaling factor regarding the difference in passive transport between *in vitro* and *in vivo*, which was obtained from approximation of the simulated and reported F_A , and psf_{passive} was set as 2.23 based on the previous report by Ando et al. (2015).

According to the definition of membrane permeability clearance in apical and basolateral membranes (Supplemental Fig. 4), $P_{\text{in vivo}}$ is equal to the passive permeability from cells to apical side (P_2), from cells to basolateral side (P_3), and from basolateral side to cells (P_4) (equation S18).

$$P_{\text{in vivo}} = P_2 = P_3 = P_4 \quad (\text{S18})$$

On the other hand, pH values in the lumen are lower than those in the enterocytes (pH 7.4), which leads to changes in the ionized fraction of the drug, depending on pKa values. In this study, it was assumed that the drug transported by passive diffusion is nonionic. Therefore, for P_1 , the membrane permeation coefficient depending on the pKa values of the drug and the pH gradients in both the lumen and enterocytes was calculated according to equation S19.

$$P_{1,z} = P_{\text{in vivo}} \frac{1 + 10^{\text{pH}_{\text{Caco-2}} - \text{pK}_{\text{aacid}} + 10^{\text{pK}_{\text{abase}} - \text{pH}_{\text{Caco-2}}}}{1 + 10^{\text{pH}_{\text{lumen,z}} - \text{pK}_{\text{aacid}} + 10^{\text{pK}_{\text{abase}} - \text{pH}_{\text{lumen,z}}}} \quad (\text{S19})$$

where $P_{1,z}$, $\text{pH}_{\text{Caco-2}}$, pK_{aacid} , and pK_{abase} represent P_1 at position z , pH in Caco-2, acid pKa, and base pKa of the drug, respectively. In this study, $\text{pH}_{\text{Caco-2}}$ was assumed to be 7.4.

Permeability on the apical ($P_{1,z}$, and P_2) and basolateral sides (P_3 and P_4) can be transferred into permeability clearance (PS) using equations S20-24.

$$PS_{\text{a,in,z}} = P_{1,z} S_{\text{abs,api}} \quad (\text{S20})$$

$$PS_{a,out,z} = P_2 S_{abs,api} + PS_{a,Pgp,z} \quad (S21)$$

$$PS_{b,in,z} = P_3 S_{abs,bas} \quad (S22)$$

$$PS_{b,out,z} = P_4 S_{abs,bas} \quad (S23)$$

$$S_{abs,api} = ME_{in\ vivo} S_{abs,bas} \quad (S24)$$

where $S_{abs,api}$, $S_{abs,bas}$, $PS_{a,Pgp,z}$, and $ME_{in\ vivo}$ represent the surface area on the apical side, surface area on the basolateral side, transport clearance by P-gp, and surface area ratio between apical and basolateral side in humans, respectively. In this study, $ME_{in\ vivo}$ was set to 20. $PS_{a,Pgp,z}$, and intrinsic clearance by CYP3A ($CL_{ent,z}$) in enterocytes were calculated using equations S25 and S26.

$$PS_{a,Pgp,z} = \frac{V_{max,Pgp} Exp_{Pgp,z} psf_{Pgp}}{K_{m,Pgp,u} + C_{ent,z}} \quad (S25)$$

$$CL_{ent,z} = \frac{V_{max,CYP3A} Exp_{CYP3A,z} psf_{CYP3A}}{K_{m,CYP3A,u} + C_{ent,z}} \quad (S26)$$

where $V_{max,Pgp}$, $V_{max,CYP3A}$, $K_{m,Pgp,u}$, $K_{m,CYP3A,u}$, psf_{Pgp} , and psf_{CYP3A} represent V_{max} for P-gp and CYP3A, K_m values based on unbound concentrations for P-gp and CYP3A, the scaling factor for transport clearance by P-gp, and intrinsic clearance by CYP3A between *in vitro* and *in vivo*, respectively. In this study, psf_{CYP3A} was assumed to be 1. Therefore, the scaling

factors used in ATOM are only $psf_{passive}$ and psf_{pgp} . The values of these parameters above were obtained from a previous report by Ando et al. (2015).

Parameter estimation of water distribution in the stomach and intestine

Water distribution was simulated in both ATOM and ACAT models by optimizing the secretion clearance and absorption rate using the reported water distribution in the stomach and small intestine after water intake by Mudie et al. (2014). Equations S27-29 were used for the simulation of water movement. The initial water volume was also obtained from the same report.

Esophagus:

$$\frac{dX_{water,es}}{dt} = -k_{es}X_{water,es} \quad (S27)$$

Stomach:

$$\frac{dX_{water,sto}}{dt} = k_{es}X_{water,es}V_{es}/V_{sto} - k_{sto}X_{water,sto} - k_{water,sto}X_{water,z} + Se_{water,sto} \quad (S28)$$

Lumen:

$$\frac{\partial X_{lum,z}}{\partial t} = D_z \frac{\partial^2 X_{lum,z}}{\partial z^2} - M_t \frac{\partial X_{lum,z}}{\partial z} - k_{water,abs}X_{water,z} + Se_{water,abs} \quad (S29)$$

where $X_{water,es}$, $X_{water,sto}$, and $X_{water,z}$ represent the amount of inflating water in the esophagus, stomach, and lumen at position z , respectively. k_{es} , k_{sto} , V_{es} , and V_{sto} represent the transit rate of drug (or water) from the esophagus to the stomach, from the stomach to the small

intestine, and volume of the esophagus and stomach, respectively. $k_{\text{water,sto}}$ and $k_{\text{water,abs}}$ are the water absorption rates in the stomach and lumen, respectively. $Se_{\text{water,sto}}$ and $Se_{\text{water,abs}}$ are water secretion clearances in the stomach and lumen, respectively. The transit rate from the esophagus to the stomach (k_{es}), water absorption rate ($k_{\text{water,sto}}$ and k_{water}), and secretion clearance ($Se_{\text{water,sto}}$ and $Se_{\text{water,z}}$) were optimized using reported luminal water volume after oral intake of 240 mL water as reported by Mudie et al. (2014). The simulated water distribution and estimated parameters are shown in Supplemental Fig. 1 and Table S1, respectively.

Sensitivity analysis of f_{ent} on the accumulation of midazolam into the portal vein in a linear condition

Sensitivity analysis of f_{ent} on drug accumulation into the portal vein was performed using pharmacokinetic parameters of midazolam with different f_{ent} values ($f_{\text{ent}} = 1, 0.5, 0.1$ and 0.01) at 0.001 mg. Simulation conditions were same with the ones in Fig. 6. In the simulation, the optimized dispersion numbers and intestinal flow rates determined using the $^{99\text{m}}\text{Tc}$ -DTPA distribution of subject A (Haruta et al., 2002) were used shown in Fig. 2A.

Estimation of pharmacokinetic parameters of midazolam, digoxin, itraconazole and clarithromycin

Distribution constants between central and peripheral compartments (k_{12} and k_{21}), distribution volume in the central compartment (V_{central}) and hepatic intrinsic clearance (CL_{int}) were optimized using the plasma concentration profile of midazolam after intravenous injection as reported by Link et al. (2008).

Regarding digoxin, V_{max} for P-gp ($V_{\text{max,Pgp}}$) was optimized by a fitting analysis to the reported F_A value in a previous report by Elmeliegy et al. (2020). Distribution constants (k_{12} ,

k_{13} , k_{21} , k_{31}) were optimized using the reported plasma concentration profile of digoxin after intravenous injection as reported by Ding et al. (2004).

Regarding itraconazole, no peripheral compartment model was applied, according to the previous report by Kudo et al. (2013). The optimization process for obtaining pharmacokinetic parameters was not conducted because all parameters were obtained from the previous reports or in silico software. Observed plasma concentration profile of itraconazole was not shown in the DI study with midazolam (Templeton et al., 2010). Therefore, the reported plasma concentration profile of itraconazole 3 days after oral administration of 100 mg twice daily in another study (Jakkola et al., 2015) was adopted for verification for predicting plasma concentration of itraconazole (Supplemental Fig. 6A).

Distribution volume in central compartment (V_{central}) were optimized using reported plasma concentration profile of clarithromycin after intravenous injection (Lappin et al., 2011). Distribution constants and intrinsic clearance of clarithromycin (k_{12} , k_{21} , CL_{int}) in oral administration were thought to be independent of that in intravenous administration because the distribution and elimination phase could not be reproduced using optimized parameters using the plasma concentration profile of clarithromycin in intravenous dosing as reported by Lappin et al. (2011). Hence, in this study, these parameters were directly optimized using the plasma concentration of clarithromycin after oral dosing. Unbound fraction in the liver (f_h) was calculated using equations S30 and S31 according to the previous reports by Kudo et al. (2013) and Poulin et al. (2002).

$$K_{p,\text{liver}} = \frac{0.02289 \cdot P + 0.72621}{0.001719 \cdot P + 0.960581} \cdot f_p / f_h \quad (\text{S30})$$

$$P = 10^{\text{Log}P} \quad (\text{S31})$$

where $K_{p,liver}$ and LogP represent liver/plasma partition coefficient and logarithm partition coefficient, respectively. Reported plasma concentration profile of clarithromycin 2 days after oral administration of 250 mg twice daily (Rengelshausen et al., 2003) was adopted for verification for predicting plasma concentration of clarithromycin (Supplemental Fig. 6B).

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Legends for Supplementary Figures

Supplemental Fig. 1 Prediction of intestinal water profile in the stomach and small intestine after a water intake of 240 mL.

Open and closed circles represent the observed water volume in the stomach and whole intestine, respectively, as reported by Mudie et al. (2014). Initial values in the stomach and small intestine were also obtained from the same report. Optimized parameters in this analysis are shown in Supplemental Table S1.

Supplemental Fig. 2 Simulated movements of ^{99m}Tc -DTPA in the gastrointestinal tract by ATOM with fixed dispersion number.

In panel A, open circles, closed circles, open squares, and open triangles represent the observed distributions in the stomach, upper intestine, lower intestine, and caecum/colon, respectively. The observed ^{99m}Tc -DTPA distribution in the lumen was obtained from a previous report by Haruta et al. (2002), which reported its distribution in two subjects. In this analysis, the observed ^{99m}Tc -DTPA distribution in the small intestine of subject A in the fasted state was used. The lines represent the simulated ^{99m}Tc -DTPA distributions in each organ. In ATOM, distributions at 40 locations were simulated, and 24 segments were assigned in the upper intestine and the other 16 segments in the lower intestine corresponding to the CATmodel using the index of the length from the inlet in the intestine. In panel B, the fixed dispersion number was optimized by fitting analysis using the luminal ^{99m}Tc -DTPA distribution of subject A in the fasted condition. The fixed dispersion number was optimized as 0.812.

Supplemental Fig. 3 Simulated movements of ^{99m}Tc -DTPA in the gastrointestinal tract using CAT model with the reported transit times to the observed distribution.

Reported transit times were referenced from a previous report by Heikkinen et al. (2012), as shown in Supplemental Table S3. Open circles, closed circles, open squares and open triangles represent the observed ^{99m}Tc -DTPA distributions in the stomach, upper intestine, lower intestine and caecum/colon, respectively, as reported by Haruta et al. (2002). The lines represent the simulated ^{99m}Tc -DTPA distributions in each organ. CAT model assumes that the small intestine is divided into six portions.

Supplemental Fig. 4 Definitions of apical and basolateral permeability.

$S_{\text{abs,api}}$ and $S_{\text{abs,bas}}$ represent the surface areas of the apical and basolateral membranes, respectively. P_1 , P_2 , P_3 , and P_4 represent the passive permeability from the lumen to enterocytes, enterocytes to the lumen, enterocytes to the lamina propria and blood capillaries, and blood capillaries to enterocytes, respectively. P_{Pgp} represents the active transport clearance of P-gp.

Supplemental Fig. 5 Effect of f_{ent} on the midazolam accumulation into the portal vein in linear conditions.

Red, blue, black and green lines represent the cumulative transfer of midazolam with $f_{\text{ent}} = 1$, 0.5, 0.1 and 0.01 into the portal vein simulated by ATOM with optimized transit times, respectively. Dose was set to 0.001 mg. The simulation was performed in the same condition with the one used in the analysis of Fig. 6.

Supplemental Fig. 6 Plasma concentration of itraconazole (A) and clarithromycin (B) in DI simulations.

In panel A, solid line represents the predicted blood concentration of itraconazole after oral administration of 100 mg twice daily. Solid circle symbol and error bars represent the mean

plasma concentration of itraconazole and the SDs reported by Jakkola et al. (2015). In panel B, solid line represents predicted plasma concentration of clarithromycin after oral administration of 250 mg twice daily. Solid circle symbol and error bars represent the mean plasma concentration of clarithromycin and the SDs reported by Rengelshausen et al. (2003).

Supplementary text 2

; Model equations used in ATOM

; Main model equation: Line 7 - 2252

; Preparative calculation equation: Line 2245 - 2845

@at 0:

; Initial water volume in the first location of the intestine

$$y1 = Wvol_int_up_r/3,$$

$$y2 = Wvol_int_up_r/3,$$

$$y3 = Wvol_int_up_r/3,$$

; Initial water volume in the second location of the intestine

$$y4 = Wvol_int_up_l/11,$$

$$y5 = Wvol_int_up_l/11,$$

$$y6 = Wvol_int_up_l/11,$$

$$y7 = Wvol_int_up_l/11,$$

$$y8 = Wvol_int_up_l/11,$$

$$y9 = Wvol_int_up_l/11,$$

$$y10 = Wvol_int_up_l/11,$$

$$y11 = Wvol_int_up_l/11,$$

$$y12 = Wvol_int_up_l/11,$$

$$y13 = Wvol_int_up_l/11,$$

$$y14 = Wvol_int_up_l/11,$$

; Initial water volume in the third location of the intestine

y15=Wvol_int_low_l/18,

y16=Wvol_int_low_l/18,

y17=Wvol_int_low_l/18,

y18=Wvol_int_low_l/18,

y19=Wvol_int_low_l/18,

y20=Wvol_int_low_l/18,

y21=Wvol_int_low_l/18,

y22=Wvol_int_low_l/18,

y23=Wvol_int_low_l/18,

y24=Wvol_int_low_l/18,

y25=Wvol_int_low_l/18,

y26=Wvol_int_low_l/18,

y27=Wvol_int_low_l/18,

y28=Wvol_int_low_l/18,

y29=Wvol_int_low_l/18,

y30=Wvol_int_low_l/18,

y31=Wvol_int_low_l/18,

y32=Wvol_int_low_l/18,

; Initial water volume in the last location of the intestine

y33=Wvol_int_low_r/8,

y34=Wvol_int_low_r/8,

y35=Wvol_int_low_r/8,

y36=Wvol_int_low_r/8,

$y_{37} = W_{vol_int_low_r}/8,$

$y_{38} = W_{vol_int_low_r}/8,$

$y_{39} = W_{vol_int_low_r}/8,$

$y_{40} = W_{vol_int_low_r}/8,$

; Initial water volume in the colon/caecum

$y_{41} = W_{vol_int_col},$

; Initial water volume in the stomach

$y_{43} = W_{vol_int},$

; Initial water volume in the whole small intestine

$y_{46} = W_{vol_int_low_l},$

; Water intake volume

$y_{50} = W_{vol_ini},$

; Concentration of perpetrator in the esophagus

$y_{320} = dose_inh/V_{es},$

; Concentration of substrate in the esophagus (administered at time=Lag)

@at Lag:

$y_{100} = dose/V_{es},$

@from 0:

; Membrane permeability of substrate

$$P_{\text{pass_lum_a1}} = P_{\text{invivo}} \frac{(1+10^{(\text{pH_Caco2}-\text{pKa_acid})}+10^{(\text{pKa_base}-\text{pH_Caco2})})}{(1+10^{(\text{pH_lum1}-\text{pKa_acid})}}$$

$$+10^{(\text{pKa_base}-\text{pH_lum1})}),$$

$$P_{\text{Spass_lum_a1}} = P_{\text{pass_lum_a1}} \text{ ME Sent1},$$

$$P_{\text{Spass_a1}} = P_{\text{invivo}} \text{ ME Sent1},$$

$$P_{\text{Spass_b1}} = P_{\text{invivo}} \text{ Sent1},$$

$$P_{\text{Sap1}} = P_{\text{Spass_lum_a1}},$$

$$P_{\text{Sbp1}} = P_{\text{Spass_b1}},$$

$$P_{\text{Sbx1}} = P_{\text{Spass_b1}},$$

$$P_{\text{Spgp1}} = \text{psf_Pgp} * V_{\text{max_Pgp}} * A_{\text{rel_Pgp1}} / (K_{\text{m_Pgp}} + \text{fent} * y_{101} / V_{\text{ent1}}),$$

$$P_{\text{Sax1}} = (P_{\text{Spass_a1}} + P_{\text{Spgp1}}),$$

$$CL1 = V_{\text{max_3A4}} * A_{\text{rel_3A4_1}}$$

$$/ (K_{\text{m_3A4}} + \text{fent} * y_{101} / V_{\text{ent1}}) / (1 + (\text{fent_inh} * y_{231} / V_{\text{ent1}}) / K_{\text{i_3A4}}),$$

$$P_{\text{pass_lum_a2}} = P_{\text{invivo}} \frac{(1+10^{(\text{pH_Caco2}-\text{pKa_acid})}+10^{(\text{pKa_base}-\text{pH_Caco2})})}{(1+10^{(\text{pH_lum2}-\text{pKa_acid})}}$$

$$+10^{(\text{pKa_base}-\text{pH_lum2})}),$$

$$P_{\text{Spass_lum_a2}} = P_{\text{pass_lum_a2}} \text{ ME Sent2},$$

$$P_{\text{Spass_a2}} = P_{\text{invivo}} \text{ ME Sent2},$$

$$P_{\text{Spass_b2}} = P_{\text{invivo}} \text{ Sent2},$$

$$P_{\text{Sap2}} = P_{\text{Spass_lum_a2}},$$

$$P_{\text{Sbp2}} = P_{\text{Spass_b2}},$$

$$P_{\text{Sbx2}} = P_{\text{Spass_b2}},$$

$$P_{\text{Spgp2}} = \text{psf_Pgp} * V_{\text{max_Pgp}} * A_{\text{rel_Pgp2}} / (K_{\text{m_Pgp}} + \text{fent} * y_{102} / V_{\text{ent2}}),$$

$$PSax2 = (PSpass_a2 + PSpgp2),$$

$$CL2 = Vmax_3A4 * Arel_3A4_2$$

$$/(Km_3A4 + fent * y102 / Vent2) / (1 + (fent_inh * y232 / Vent2) / Ki_3A4),$$

$$Ppass_lum_a3 = P_invivo (1 + 10^{(pH_Caco2 - pKa_acid)} + 10^{(pKa_base - pH_Caco2)}) / (1 + 10^{(pH_lum3 - pKa_acid)}$$

$$+ 10^{(pKa_base - pH_lum3)}),$$

$$PSpass_lum_a3 = Ppass_lum_a3 ME Sent3,$$

$$PSpass_a3 = P_invivo ME Sent3,$$

$$PSpass_b3 = P_invivo Sent3,$$

$$PSap3 = PSpass_lum_a3,$$

$$PSbp3 = PSpass_b3,$$

$$PSbx3 = PSpass_b3,$$

$$PSpgp3 = psf_Pgp Vmax_Pgp Arel_Pgp3 / (Km_Pgp + fent y103 / Vent3),$$

$$PSax3 = (PSpass_a3 + PSpgp3),$$

$$CL3 = Vmax_3A4 Arel_3A4_3 / (Km_3A4 + fent y103 / Vent3) / (1 + (fent_inh * y233 / Vent3) / Ki_3A4),$$

$$Ppass_lum_a4 = P_invivo (1 + 10^{(pH_Caco2 - pKa_acid)} + 10^{(pKa_base - pH_Caco2)}) / (1 + 10^{(pH_lum4 - pKa_acid)} + 10^{(pKa_base - pH_lum4)}),$$

$$PSpass_a4 = P_invivo ME Sent4,$$

$$PSpass_b4 = P_invivo Sent4,$$

$$PSpass_lum_a4 = Ppass_lum_a4 ME Sent4,$$

$$PSap4 = PSpass_lum_a4,$$

$$PSbp4 = PSpass_b4,$$

$$PSbx4 = PSpass_b4,$$

$$PSpgp4 = psf_Pgp \text{ Vmax_Pgp Arel_Pgp4 } / (Km_Pgp + fent \text{ y104/Vent4}),$$

$$PSax4 = (PSpass_a4 + PSpgp4),$$

$$CL4 = \text{ Vmax_3A4 Arel_3A4_4 } / (Km_3A4 + fent \text{ y104/Vent4}) / (1 + (fent_inh * y234/Vent4) / Ki_3A4),$$

$$Ppass_lum_a5 = P_invivo (1 + 10^{(pH_Caco2 - pKa_acid)} + 10^{(pKa_base - pH_Caco2)}) / (1 + 10^{(pH_lum5 - pKa_acid)} + 10^{(pKa_base - pH_lum5)}),$$

$$PSpass_a5 = P_invivo \text{ ME Sent5},$$

$$PSpass_b5 = P_invivo \text{ Sent5},$$

$$PSpass_lum_a5 = Ppass_lum_a5 \text{ ME Sent5},$$

$$PSap5 = PSpass_lum_a5,$$

$$PSbp5 = PSpass_b5,$$

$$PSbx5 = PSpass_b5,$$

$$PSpgp5 = psf_Pgp \text{ Vmax_Pgp Arel_Pgp5 } / (Km_Pgp + fent \text{ y105/Vent5}),$$

$$PSax5 = (PSpass_a5 + PSpgp5),$$

$$CL5 = \text{ Vmax_3A4 Arel_3A4_5 } / (Km_3A4 + fent \text{ y105/Vent5}) / (1 + (fent_inh * y235/Vent5) / Ki_3A4),$$

$$Ppass_lum_a6 = P_invivo (1 + 10^{(pH_Caco2 - pKa_acid)} + 10^{(pKa_base - pH_Caco2)}) / (1 + 10^{(pH_lum6 - pKa_acid)} + 10^{(pKa_base - pH_lum6)}),$$

$$PSpass_a6 = P_invivo \text{ ME Sent6},$$

$$PSpass_b6 = P_invivo \text{ Sent6},$$

$$PSpass_lum_a6 = Ppass_lum_a6 \text{ ME Sent6},$$

$$PSap6 = PSpass_lum_a6,$$

$$PSbp6 = PSpass_b6,$$

$$PSbx6 = PSpass_b6,$$

$$PSpgp6 = psf_Pgp \text{ Vmax_Pgp Arel_Pgp6 } / (Km_Pgp + fent \text{ y106/Vent6}),$$

$$PSax6 = (PSpass_a6 + PSpgp6),$$

$$CL6 = \text{ Vmax_3A4 Arel_3A4_6 } / (Km_3A4 + fent \text{ y106/Vent6}) / (1 + (fent_inh * y236/Vent6) / Ki_3A4),$$

$$Ppass_lum_a7 = P_invivo (1 + 10^{(pH_Caco2 - pKa_acid)} + 10^{(pKa_base - pH_Caco2)}) / (1 + 10^{(pH_lum7 - pKa_acid)} + 10^{(pKa_base - pH_lum7)}),$$

$$PSpass_a7 = P_invivo \text{ ME Sent7},$$

$$PSpass_b7 = P_invivo \text{ Sent7},$$

$$PSpass_lum_a7 = Ppass_lum_a7 \text{ ME Sent7},$$

$$PSap7 = PSpass_lum_a7,$$

$$PSbp7 = PSpass_b7,$$

$$PSbx7 = PSpass_b7,$$

$$PSpgp7 = psf_Pgp \text{ Vmax_Pgp Arel_Pgp7 } / (Km_Pgp + fent \text{ y107/Vent7}),$$

$$PSax7 = (PSpass_a7 + PSpgp7),$$

$$CL7 = \text{ Vmax_3A4 Arel_3A4_7 } / (Km_3A4 + fent \text{ y107/Vent7}) / (1 + (fent_inh * y237/Vent7) / Ki_3A4),$$

$$Ppass_lum_a8 = P_invivo (1 + 10^{(pH_Caco2 - pKa_acid)} + 10^{(pKa_base - pH_Caco2)}) / (1 + 10^{(pH_lum8 - pKa_acid)} + 10^{(pKa_base - pH_lum8)}),$$

$$PSpass_a8 = P_invivo \text{ ME Sent8},$$

$$PSpass_b8 = P_invivo \text{ Sent8},$$

$$PSpass_lum_a8 = Ppass_lum_a8 \text{ ME Sent8},$$

$$PSap8 = PSp_{pass_lum_a4},$$

$$PSbp8 = PSp_{pass_b8},$$

$$PSbx8 = (PSp_{pass_b8}),$$

$$PSpgp8 = \text{psf_Pgp } V_{max_Pgp} A_{rel_Pgp8} / (K_{m_Pgp} + f_{ent} y_{108} / V_{ent8}),$$

$$PSax8 = (PSp_{pass_a8} + PSpgp8),$$

$$CL8 = \frac{V_{max_3A4} A_{rel_3A4_8}}{(K_{m_3A4} + f_{ent} y_{108} / V_{ent8}) (1 + (f_{ent_inh} * y_{238} / V_{ent8}) / K_{i_3A4})},$$

$$P_{pass_lum_a9} = P_{invivo} \frac{(1 + 10^{(pH_Caco2 - pK_{a_acid})} + 10^{(pK_{a_base} - pH_Caco2)})}{(1 + 10^{(pH_lum9 - pK_{a_acid})} + 10^{(pK_{a_base} - pH_lum9)})},$$

$$PSp_{pass_a9} = P_{invivo} ME_{Sent9},$$

$$PSp_{pass_b9} = P_{invivo} Sent9,$$

$$PSp_{pass_lum_a9} = P_{pass_lum_a9} ME_{Sent9},$$

$$PSap9 = PSp_{pass_lum_a9},$$

$$PSbp9 = PSp_{pass_b9},$$

$$PSbx9 = PSp_{pass_b9},$$

$$PSpgp9 = \text{psf_Pgp } V_{max_Pgp} A_{rel_Pgp9} / (K_{m_Pgp} + f_{ent} y_{109} / V_{ent9}),$$

$$PSax9 = (PSp_{pass_a9} + PSpgp9),$$

$$CL9 = \frac{V_{max_3A4} A_{rel_3A4_9}}{(K_{m_3A4} + f_{ent} y_{109} / V_{ent9}) (1 + (f_{ent_inh} * y_{239} / V_{ent9}) / K_{i_3A4})},$$

$$P_{pass_lum_a10} = P_{invivo} \frac{(1 + 10^{(pH_Caco2 - pK_{a_acid})} + 10^{(pK_{a_base} - pH_Caco2)})}{(1 + 10^{(pH_lum10 - pK_{a_acid})} + 10^{(pK_{a_base} - pH_lum10)})},$$

$$PSp_{pass_a10} = P_{invivo} ME_{Sent10},$$

$$PSp_{pass_b10} = P_{invivo} Sent10,$$

$PS_{pass_lum_a10} = P_{pass_lum_a10} ME_{Sent10}$,
 $PS_{ap10} = PS_{pass_lum_a10}$,
 $PS_{bp10} = PS_{pass_b10}$,
 $PS_{bx10} = PS_{pass_b10}$,
 $PS_{pgp10} = psf_Pgp \frac{V_{max_Pgp} A_{rel_Pgp10}}{(K_{m_Pgp} + f_{ent} y_{110}/V_{ent10})}$,
 $PS_{ax10} = (PS_{pass_a10} + PS_{pgp10})$,
 $CL_{10} = \frac{V_{max_3A4} A_{rel_3A4_10}}{(K_{m_3A4} + f_{ent} y_{110}/V_{ent10}) / (1 + (f_{ent_inh} * y_{240}/V_{ent10}) / K_{i_3A4})}$,

$P_{pass_lum_a11} = P_{invivo} \frac{(1 + 10^{(pH_{Caco2} - pK_{a_acid})} + 10^{(pK_{a_base} - pH_{Caco2})})}{(1 + 10^{(pH_{lum11} - pK_{a_acid})} + 10^{(pK_{a_base} - pH_{lum11})})}$,
 $PS_{pass_a11} = P_{invivo} ME_{Sent11}$,
 $PS_{pass_b11} = P_{invivo} Sent_{11}$,
 $PS_{pass_lum_a11} = P_{pass_lum_a11} ME_{Sent11}$,
 $PS_{ap11} = PS_{pass_lum_a11}$,
 $PS_{bp11} = PS_{pass_b11}$,
 $PS_{bx11} = PS_{pass_b11}$,
 $PS_{pgp11} = psf_Pgp \frac{V_{max_Pgp} A_{rel_Pgp11}}{(K_{m_Pgp} + f_{ent} y_{111}/V_{ent11})}$,
 $PS_{ax11} = (PS_{pass_a11} + PS_{pgp11})$,
 $CL_{11} = \frac{V_{max_3A4} A_{rel_3A4_11}}{(K_{m_3A4} + f_{ent} y_{111}/V_{ent11}) / (1 + (f_{ent_inh} * y_{241}/V_{ent11}) / K_{i_3A4})}$,

$P_{pass_lum_a12} = P_{invivo} \frac{(1 + 10^{(pH_{Caco2} - pK_{a_acid})} + 10^{(pK_{a_base} - pH_{Caco2})})}{(1 + 10^{(pH_{lum12} - pK_{a_acid})} + 10^{(pK_{a_base} - pH_{lum12})})}$,
 $PS_{pass_a12} = P_{invivo} ME_{Sent12}$,

$$PSpass_b12 = P_invivo \text{ Sent12},$$

$$PSpass_lum_a12 = Ppass_lum_a12 \text{ ME Sent12},$$

$$PSap12 = PSpass_lum_a12,$$

$$PSbp12 = PSpass_b12,$$

$$PSbx12 = PSpass_b12,$$

$$PSpgp12 = psf_Pgp \text{ Vmax_Pgp Arel_Pgp12 } / (Km_Pgp + fent \text{ y112/Vent12}),$$

$$PSax12 = (PSpass_a12 + PSpgp12),$$

$$CL12 = \text{ Vmax_3A4 Arel_3A4_12 } / (Km_3A4 + fent \text{ y112/Vent12}) / (1 + (fent_inh * y242 / Vent12) / Ki_3A4),$$

$$Ppass_lum_a13 = P_invivo (1 + 10^{(pH_Caco2 - pKa_acid)} + 10^{(pKa_base - pH_Caco2)}) / (1 + 10^{(pH_lum13 - pKa_acid)} + 10^{(pKa_base - pH_lum13)}),$$

$$PSpass_a13 = P_invivo \text{ ME Sent13},$$

$$PSpass_b13 = P_invivo \text{ Sent13},$$

$$PSpass_lum_a13 = Ppass_lum_a13 \text{ ME Sent13},$$

$$PSap13 = PSpass_lum_a13,$$

$$PSbp13 = PSpass_b13,$$

$$PSbx13 = PSpass_b13,$$

$$PSpgp13 = psf_Pgp \text{ Vmax_Pgp Arel_Pgp13 } / (Km_Pgp + fent \text{ y113/Vent13}),$$

$$PSax13 = (PSpass_a13 + PSpgp13),$$

$$CL13 = \text{ Vmax_3A4 Arel_3A4_13 } / (Km_3A4 + fent \text{ y113/Vent13}) / (1 + (fent_inh * y243 / Vent13) / Ki_3A4),$$

$$Ppass_lum_a14 = P_invivo (1 + 10^{(pH_Caco2 - pKa_acid)} + 10^{(pKa_base - pH_Caco2)}) / (1 + 10^{(pH_lum14 - pKa_acid)} + 10^{(pKa_base - pH_lum14)}),$$

$$P_{Spa_{a14}} = P_{invivo} ME_{Sent14},$$

$$P_{Spa_{b14}} = P_{invivo} Sent14,$$

$$P_{Spa_{lum_{a14}}} = P_{pass_{lum_{a14}}} ME_{Sent14},$$

$$P_{Sap14} = P_{Spa_{lum_{a14}}},$$

$$P_{Sbp14} = P_{Spa_{b14}},$$

$$P_{Sbx14} = P_{Spa_{b14}},$$

$$P_{Spgp14} = \frac{psf_{Pgp} V_{max_{Pgp}} A_{rel_{Pgp14}}}{(K_{m_{Pgp}} + f_{ent} y_{114}/V_{ent14})},$$

$$P_{Sax14} = (P_{Spa_{a14}} + P_{Spgp14}),$$

$$CL_{14} = \frac{V_{max_{3A4}} A_{rel_{3A4_{14}}}}{(K_{m_{3A4}} + f_{ent} y_{114}/V_{ent14}) / (1 + (f_{ent_inh} * y_{244}/V_{ent14}) / K_{i_{3A4}})},$$

$$P_{pass_{lum_{a15}}} = P_{invivo} \frac{(1 + 10^{(pH_{Caco2} - pK_{a_{acid}})} + 10^{(pK_{a_{base}} - pH_{Caco2})})}{(1 + 10^{(pH_{lum15} - pK_{a_{acid}})} + 10^{(pK_{a_{base}} - pH_{lum15})})},$$

$$P_{Spa_{a15}} = P_{invivo} ME_{Sent15},$$

$$P_{Spa_{b15}} = P_{invivo} Sent15,$$

$$P_{Spa_{lum_{a15}}} = P_{pass_{lum_{a15}}} ME_{Sent15},$$

$$P_{Sap15} = P_{Spa_{lum_{a15}}},$$

$$P_{Sbp15} = P_{Spa_{b15}},$$

$$P_{Sbx15} = P_{Spa_{b15}},$$

$$P_{Spgp15} = \frac{psf_{Pgp} V_{max_{Pgp}} A_{rel_{Pgp15}}}{(K_{m_{Pgp}} + f_{ent} y_{115}/V_{ent15})},$$

$$P_{Sax15} = (P_{Spa_{a15}} + P_{Spgp15}),$$

$$CL_{15} = \frac{V_{max_{3A4}} A_{rel_{3A4_{15}}}}{(K_{m_{3A4}} + f_{ent} y_{115}/V_{ent15}) / (1 + (f_{ent_inh} * y_{245}/V_{ent15}) / K_{i_{3A4}})},$$

$$P_{\text{pass_lum_a16}} = P_{\text{invivo}} \frac{(1+10^{(\text{pH_Caco2}-\text{pKa_acid})}+10^{(\text{pKa_base}-\text{pH_Caco2})})}{(1+10^{(\text{pH_lum16}-\text{pKa_acid})}+10^{(\text{pKa_base}-\text{pH_lum16})})},$$

$$P_{\text{Spass_a16}} = P_{\text{invivo}} \text{ME Sent16},$$

$$P_{\text{Spass_b16}} = P_{\text{invivo}} \text{Sent16},$$

$$P_{\text{Spass_lum_a16}} = P_{\text{pass_lum_a16}} \text{ME Sent16},$$

$$P_{\text{Sap16}} = P_{\text{Spass_lum_a16}},$$

$$P_{\text{Sbp16}} = P_{\text{Spass_b16}},$$

$$P_{\text{Sbx16}} = P_{\text{Spass_b16}},$$

$$P_{\text{Spgp16}} = \text{psf_Pgp} \frac{V_{\text{max_Pgp}} \text{Arel_Pgp16}}{(K_{\text{m_Pgp}} + \text{fent y116}/V_{\text{ent16}})},$$

$$P_{\text{Sax16}} = (P_{\text{Spass_a16}} + P_{\text{Spgp16}}),$$

$$CL_{16} = \frac{V_{\text{max_3A4}} \text{Arel_3A4_16}}{(K_{\text{m_3A4}} + \text{fent y116}/V_{\text{ent16}}) / (1 + (\text{fent_inh} * y_{246}/V_{\text{ent16}}) / K_{\text{i_3A4}})},$$

$$P_{\text{pass_lum_a17}} = P_{\text{invivo}} \frac{(1+10^{(\text{pH_Caco2}-\text{pKa_acid})}+10^{(\text{pKa_base}-\text{pH_Caco2})})}{(1+10^{(\text{pH_lum17}-\text{pKa_acid})}+10^{(\text{pKa_base}-\text{pH_lum17})})},$$

$$P_{\text{Spass_a17}} = P_{\text{invivo}} \text{ME Sent17},$$

$$P_{\text{Spass_b17}} = P_{\text{invivo}} \text{Sent17},$$

$$P_{\text{Spass_lum_a17}} = P_{\text{pass_lum_a17}} \text{ME Sent17},$$

$$P_{\text{Sap17}} = P_{\text{Spass_lum_a17}},$$

$$P_{\text{Sbp17}} = P_{\text{Spass_b17}},$$

$$P_{\text{Sbx17}} = P_{\text{Spass_b17}},$$

$$P_{\text{Spgp17}} = \text{psf_Pgp} \frac{V_{\text{max_Pgp}} \text{Arel_Pgp17}}{(K_{\text{m_Pgp}} + \text{fent y117}/V_{\text{ent17}})},$$

$$P_{\text{Sax17}} = (P_{\text{Spass_a17}} + P_{\text{Spgp17}}),$$

$$CL_{17} = \frac{V_{\text{max_3A4}} \text{Arel_3A4_17}}{(K_{\text{m_3A4}} + \text{fent y117}/V_{\text{ent17}}) / (1 + (\text{fent_inh} * y_{247}/V_{\text{ent17}}) / K_{\text{i_3A4}})},$$

$$P_{pass_lum_a18} = P_{invivo} \frac{(1+10^{(pH_Caco2-pKa_acid)}+10^{(pKa_base-pH_Caco2)})}{(1+10^{(pH_lum18-pKa_acid)}+10^{(pKa_base-pH_lum18)})}$$
,

$$P_{Spass_a18} = P_{invivo} ME_{Sent18}$$
,

$$P_{Spass_b18} = P_{invivo} Sent18$$
,

$$P_{Spass_lum_a18} = P_{pass_lum_a18} ME_{Sent18}$$
,

$$P_{Sap18} = P_{Spass_lum_a18}$$
,

$$P_{Sbp18} = P_{Spass_b18}$$
,

$$P_{Sbx18} = P_{Spass_b18}$$
,

$$P_{Spgp18} = psf_Pgp \frac{Vmax_Pgp Arel_Pgp18}{(Km_Pgp+fent y118/Vent18)}$$
,

$$P_{Sax18} = (P_{Spass_a18} + P_{Spgp18})$$
,

$$CL18 = \frac{Vmax_3A4 Arel_3A4_18}{(Km_3A4+fent y118/Vent18)/(1+(fent_inh*y248/Vent18)/Ki_3A4)}$$
,

$$P_{pass_lum_a19} = P_{invivo} \frac{(1+10^{(pH_Caco2-pKa_acid)}+10^{(pKa_base-pH_Caco2)})}{(1+10^{(pH_lum19-pKa_acid)}+10^{(pKa_base-pH_lum19)})}$$
,

$$P_{Spass_a19} = P_{invivo} ME_{Sent19}$$
,

$$P_{Spass_b19} = P_{invivo} Sent19$$
,

$$P_{Spass_lum_a19} = P_{pass_lum_a19} ME_{Sent19}$$
,

$$P_{Sap19} = P_{Spass_lum_a19}$$
,

$$P_{Sbp19} = P_{Spass_b19}$$
,

$$P_{Sbx19} = P_{Spass_b19}$$
,

$$P_{Spgp19} = psf_Pgp \frac{Vmax_Pgp Arel_Pgp19}{(Km_Pgp+fent y119/Vent19)}$$
,

$$P_{Sax19} = (P_{Spass_a19} + P_{Spgp19})$$
,

$$CL19 = \frac{V_{max_3A4} A_{rel_3A4_19}}{(K_{m_3A4} + f_{ent} y_{119}/V_{ent19}) / (1 + (f_{ent_inh} * y_{249}/V_{ent19}) / K_{i_3A4})}$$

$$P_{pass_lum_a20} = P_{invivo} \frac{(1 + 10^{(pH_Caco2 - pK_{a_acid})}) + 10^{(pK_{a_base} - pH_Caco2)}}{(1 + 10^{(pH_lum20 - pK_{a_acid})}) + 10^{(pK_{a_base} - pH_lum20)}}$$

$$P_{Spass_a20} = P_{invivo} ME_{Sent20}$$

$$P_{Spass_b20} = P_{invivo} Sent20$$

$$P_{Spass_lum_a20} = P_{pass_lum_a20} ME_{Sent20}$$

$$P_{Sap20} = P_{Spass_lum_a20}$$

$$P_{Sbp20} = P_{Spass_b20}$$

$$P_{Sbx20} = P_{Spass_b20}$$

$$P_{Spgp20} = \frac{psf_Pgp V_{max_Pgp} A_{rel_Pgp20}}{(K_{m_Pgp} + f_{ent} y_{120}/V_{ent20})}$$

$$P_{Sax20} = (P_{Spass_a20} + P_{Spgp20})$$

$$CL20 = \frac{V_{max_3A4} A_{rel_3A4_20}}{(K_{m_3A4} + f_{ent} y_{120}/V_{ent20}) / (1 + (f_{ent_inh} * y_{250}/V_{ent20}) / K_{i_3A4})}$$

$$P_{pass_lum_a21} = P_{invivo} \frac{(1 + 10^{(pH_Caco2 - pK_{a_acid})}) + 10^{(pK_{a_base} - pH_Caco2)}}{(1 + 10^{(pH_lum21 - pK_{a_acid})}) + 10^{(pK_{a_base} - pH_lum21)}}$$

$$P_{Spass_a21} = P_{invivo} ME_{Sent21}$$

$$P_{Spass_b21} = P_{invivo} Sent21$$

$$P_{Spass_lum_a21} = P_{pass_lum_a21} ME_{Sent21}$$

$$P_{Sap21} = P_{Spass_lum_a21}$$

$$P_{Sbp21} = P_{Spass_b21}$$

$$P_{Sbx21} = P_{Spass_b21}$$

$$P_{Spgp21} = \frac{psf_Pgp V_{max_Pgp} A_{rel_Pgp21}}{(K_{m_Pgp} + f_{ent} y_{121}/V_{ent21})}$$

$$PSax21 = (PSpass_a21 + PSpgp21),$$

$$CL21 = \frac{Vmax_3A4 \text{ Arel_3A4_21}}{(Km_3A4 + fent y121/Vent21) / (1 + (fent_inh * y251/Vent21) / Ki_3A4)},$$

$$Ppass_lum_a22 = P_invivo \frac{(1 + 10^{(pH_Caco2 - pKa_acid)} + 10^{(pKa_base - pH_Caco2)})}{(1 + 10^{(pH_lum22 - pKa_acid)} + 10^{(pKa_base - pH_lum22)}),$$

$$PSpass_a22 = P_invivo \text{ ME Sent22},$$

$$PSpass_b22 = P_invivo \text{ Sent22},$$

$$PSpass_lum_a22 = Ppass_lum_a22 \text{ ME Sent22},$$

$$PSap22 = PSpass_lum_a22,$$

$$PSbp22 = PSpass_b22,$$

$$PSbx22 = PSpass_b22,$$

$$PSpgp22 = psf_Pgp \frac{Vmax_Pgp \text{ Arel_Pgp22}}{(Km_Pgp + fent y122/Vent22)},$$

$$PSax22 = (PSpass_a22 + PSpgp22),$$

$$CL22 = \frac{Vmax_3A4 \text{ Arel_3A4_22}}{(Km_3A4 + fent y122/Vent22) / (1 + (fent_inh * y252/Vent22) / Ki_3A4)},$$

$$Ppass_lum_a23 = P_invivo \frac{(1 + 10^{(pH_Caco2 - pKa_acid)} + 10^{(pKa_base - pH_Caco2)})}{(1 + 10^{(pH_lum23 - pKa_acid)} + 10^{(pKa_base - pH_lum23)}),$$

$$PSpass_a23 = P_invivo \text{ ME Sent23},$$

$$PSpass_b23 = P_invivo \text{ Sent23},$$

$$PSpass_lum_a23 = Ppass_lum_a23 \text{ ME Sent23},$$

$$PSap23 = PSpass_lum_a23,$$

$$PSbp23 = PSpass_b23,$$

$$PSbx23 = PSpass_b23,$$

$$PSpgp23 = \text{psf_Pgp} \text{ Vmax_Pgp} \text{ Arel_Pgp23} / (\text{Km_Pgp} + \text{fent} \text{ y123} / \text{Vent23}),$$

$$PSax23 = (\text{PSpass_a23} + \text{PSpgp23}),$$

$$\text{CL23} = \text{Vmax_3A4} \text{ Arel_3A4_23} / (\text{Km_3A4} + \text{fent} \text{ y123} / \text{Vent23}) / (1 + (\text{fent_inh} * \text{y253} / \text{Vent23}) / \text{Ki_3A4}),$$

$$\text{Ppass_lum_a24} = \text{P_invivo} (1 + 10^{(\text{pH_Caco2} - \text{pKa_acid})} + 10^{(\text{pKa_base} - \text{pH_Caco2})}) / (1 + 10^{(\text{pH_lum24} - \text{pKa_acid})} + 10^{(\text{pKa_base} - \text{pH_lum24})}),$$

$$\text{PSpass_a24} = \text{P_invivo} \text{ ME} \text{ Sent24},$$

$$\text{PSpass_b24} = \text{P_invivo} \text{ Sent24},$$

$$\text{PSpass_lum_a24} = \text{Ppass_lum_a24} \text{ ME} \text{ Sent24},$$

$$\text{PSap24} = \text{PSpass_lum_a24},$$

$$\text{PSbp24} = \text{PSpass_b24},$$

$$\text{PSbx24} = \text{PSpass_b24},$$

$$\text{PSpgp24} = \text{psf_Pgp} \text{ Vmax_Pgp} \text{ Arel_Pgp24} / (\text{Km_Pgp} + \text{fent} \text{ y124} / \text{Vent24}),$$

$$\text{PSax24} = (\text{PSpass_a24} + \text{PSpgp24}),$$

$$\text{CL24} = \text{Vmax_3A4} \text{ Arel_3A4_24} / (\text{Km_3A4} + \text{fent} \text{ y124} / \text{Vent24}) / (1 + (\text{fent_inh} * \text{y254} / \text{Vent24}) / \text{Ki_3A4}),$$

$$\text{Ppass_lum_a25} = \text{P_invivo} (1 + 10^{(\text{pH_Caco2} - \text{pKa_acid})} + 10^{(\text{pKa_base} - \text{pH_Caco2})}) / (1 + 10^{(\text{pH_lum25} - \text{pKa_acid})} + 10^{(\text{pKa_base} - \text{pH_lum25})}),$$

$$\text{PSpass_a25} = \text{P_invivo} \text{ ME} \text{ Sent25},$$

$$\text{PSpass_b25} = \text{P_invivo} \text{ Sent25},$$

$$\text{PSpass_lum_a25} = \text{Ppass_lum_a25} \text{ ME} \text{ Sent25},$$

$$\text{PSap25} = \text{PSpass_lum_a25},$$

$$\text{PSbp25} = \text{PSpass_b25},$$

$$PSbx25 = PSpass_b25,$$

$$PSpgp25 = psf_Pgp \frac{Vmax_Pgp \ Arel_Pgp25}{(Km_Pgp + fent \ y125/Vent25)},$$

$$PSax25 = (PSpass_a25 + PSpgp25),$$

$$CL25 = \frac{Vmax_3A4 \ Arel_3A4_25}{(Km_3A4 + fent \ y125/Vent25) / (1 + (fent_inh * y255/Vent25) / Ki_3A4)},$$

$$Ppass_lum_a26 = P_invivo \frac{(1 + 10^{(pH_Caco2 - pKa_acid)} + 10^{(pKa_base - pH_Caco2)})}{(1 + 10^{(pH_lum26 - pKa_acid)} + 10^{(pKa_base - pH_lum26)}),$$

$$PSpass_a26 = P_invivo \ ME \ Sent26,$$

$$PSpass_b26 = P_invivo \ Sent26,$$

$$PSpass_lum_a26 = Ppass_lum_a26 \ ME \ Sent26,$$

$$PSap26 = PSpass_lum_a26,$$

$$PSbp26 = PSpass_b26,$$

$$PSbx26 = PSpass_b26,$$

$$PSpgp26 = psf_Pgp \frac{Vmax_Pgp \ Arel_Pgp26}{(Km_Pgp + fent \ y126/Vent26)},$$

$$PSax26 = (PSpass_a26 + PSpgp26),$$

$$CL26 = \frac{Vmax_3A4 \ Arel_3A4_26}{(Km_3A4 + fent \ y126/Vent26) / (1 + (fent_inh * y256/Vent26) / Ki_3A4)},$$

$$Ppass_lum_a27 = P_invivo \frac{(1 + 10^{(pH_Caco2 - pKa_acid)} + 10^{(pKa_base - pH_Caco2)})}{(1 + 10^{(pH_lum27 - pKa_acid)} + 10^{(pKa_base - pH_lum27)}),$$

$$PSpass_a27 = P_invivo \ ME \ Sent27,$$

$$PSpass_b27 = P_invivo \ Sent27,$$

$$PSpass_lum_a27 = Ppass_lum_a27 \ ME \ Sent27,$$

$$PSap27 = PSpass_lum_a27,$$

$$PSbp27 = PSpass_b27,$$

$$PSbx27 = PSpass_b27,$$

$$PSpgp27 = psf_Pgp \text{ Vmax_Pgp Arel_Pgp27 } / (Km_Pgp + fent \ y127 / Vent27),$$

$$PSax27 = (PSpass_a27 + PSpgp27),$$

$$CL27 = \text{ Vmax_3A4 Arel_3A4_27 } / (Km_3A4 + fent \ y127 / Vent27) / (1 + (fent_inh * y257 / Vent27) / Ki_3A4),$$

$$Ppass_lum_a28 = P_invivo (1 + 10^{(pH_Caco2 - pKa_acid)} + 10^{(pKa_base - pH_Caco2)}) / (1 + 10^{(pH_lum28 - pKa_acid)} + 10^{(pKa_base - pH_lum28)}),$$

$$PSpass_a28 = P_invivo \text{ ME Sent28},$$

$$PSpass_b28 = P_invivo \text{ Sent28},$$

$$PSpass_lum_a28 = Ppass_lum_a28 \text{ ME Sent28},$$

$$PSap28 = PSpass_lum_a28,$$

$$PSbp28 = PSpass_b28,$$

$$PSbx28 = PSpass_b28,$$

$$PSpgp28 = psf_Pgp \text{ Vmax_Pgp Arel_Pgp28 } / (Km_Pgp + fent \ y128 / Vent28),$$

$$PSax28 = (PSpass_a28 + PSpgp28),$$

$$CL28 = \text{ Vmax_3A4 Arel_3A4_28 } / (Km_3A4 + fent \ y128 / Vent28) / (1 + (fent_inh * y258 / Vent28) / Ki_3A4),$$

$$Ppass_lum_a29 = P_invivo (1 + 10^{(pH_Caco2 - pKa_acid)} + 10^{(pKa_base - pH_Caco2)}) / (1 + 10^{(pH_lum29 - pKa_acid)} + 10^{(pKa_base - pH_lum29)}),$$

$$PSpass_a29 = P_invivo \text{ ME Sent29},$$

$$PSpass_b29 = P_invivo \text{ Sent29},$$

$$PSpass_lum_a29 = Ppass_lum_a29 \text{ ME Sent29},$$

$$PSap29 = PSpass_lum_a29,$$

$$PSbp29 = PSpass_b29,$$

$$PSbx29 = PSpass_b29,$$

$$PSpgp29 = psf_Pgp \text{ Vmax_Pgp Arel_Pgp29 } / (Km_Pgp + fent \ y129 / Vent29),$$

$$PSax29 = (PSpass_a29 + PSpgp29),$$

$$CL29 = \text{ Vmax_3A4 Arel_3A4_29 } / (Km_3A4 + fent$$

$$y129 / Vent29) / (1 + (fent_inh * y259 / Vent29) / Ki_3A4),$$

$$Ppass_lum_a30 = P_invivo (1 + 10^{(pH_Caco2 - pKa_acid)} + 10^{(pKa_base - pH_Caco2)}) / (1 + 10^{(pH_lum30 - pKa_acid)} + 10^{(pKa_base - pH_lum30)}),$$

$$PSpass_a30 = P_invivo \text{ ME Sent30},$$

$$PSpass_b30 = P_invivo \text{ Sent30},$$

$$PSpass_lum_a30 = Ppass_lum_a30 \text{ ME Sent30},$$

$$PSap30 = PSpass_lum_a30,$$

$$PSbp30 = PSpass_b30,$$

$$PSbx30 = PSpass_b30,$$

$$PSpgp30 = psf_Pgp \text{ Vmax_Pgp Arel_Pgp30 } / (Km_Pgp + fent \ y130 / Vent30),$$

$$PSax30 = (PSpass_a30 + PSpgp30),$$

$$CL30 = \text{ Vmax_3A4 Arel_3A4_30 } / (Km_3A4 + fent$$

$$y130 / Vent30) / (1 + (fent_inh * y260 / Vent30) / Ki_3A4),$$

$$Ppass_lum_a31 = P_invivo (1 + 10^{(pH_Caco2 - pKa_acid)} + 10^{(pKa_base - pH_Caco2)}) / (1 + 10^{(pH_lum31 - pKa_acid)} + 10^{(pKa_base - pH_lum31)}),$$

$$PSpass_a31 = P_invivo \text{ ME Sent31},$$

$$PSpass_b31 = P_invivo \text{ Sent31},$$

$PS_{pass_lum_a31} = P_{pass_lum_a31} ME_{Sent31}$,
 $PS_{ap31} = PS_{pass_lum_a31}$,
 $PS_{bp31} = PS_{pass_b31}$,
 $PS_{bx31} = PS_{pass_b31}$,
 $PS_{pgp31} = \frac{psf_Pgp V_{max_Pgp} A_{rel_Pgp31}}{(K_{m_Pgp} + f_{ent} y_{131}/V_{ent31})}$,
 $PS_{ax31} = (PS_{pass_a31} + PS_{pgp31})$,
 $CL_{31} = \frac{V_{max_3A4} A_{rel_3A4_31}}{(K_{m_3A4} + f_{ent} y_{131}/V_{ent31}) / (1 + (f_{ent_inh} * y_{261}/V_{ent31}) / K_{i_3A4})}$,

$P_{pass_lum_a32} = P_{invivo} \frac{(1 + 10^{(pH_{Caco2} - pK_{a_acid})} + 10^{(pK_{a_base} - pH_{Caco2})})}{(1 + 10^{(pH_{lum32} - pK_{a_acid})} + 10^{(pK_{a_base} - pH_{lum32})})}$,
 $PS_{pass_a32} = P_{invivo} ME_{Sent32}$,
 $PS_{pass_b32} = P_{invivo} Sent_{32}$,
 $PS_{pass_lum_a32} = P_{pass_lum_a32} ME_{Sent32}$,
 $PS_{ap32} = PS_{pass_lum_a32}$,
 $PS_{bp32} = PS_{pass_b32}$,
 $PS_{bx32} = PS_{pass_b32}$,
 $PS_{pgp32} = \frac{psf_Pgp V_{max_Pgp} A_{rel_Pgp32}}{(K_{m_Pgp} + f_{ent} y_{132}/V_{ent32})}$,
 $PS_{ax32} = (PS_{pass_a32} + PS_{pgp32})$,
 $CL_{32} = \frac{V_{max_3A4} A_{rel_3A4_32}}{(K_{m_3A4} + f_{ent} y_{132}/V_{ent32}) / (1 + (f_{ent_inh} * y_{262}/V_{ent32}) / K_{i_3A4})}$,

$P_{pass_lum_a33} = P_{invivo} \frac{(1 + 10^{(pH_{Caco2} - pK_{a_acid})} + 10^{(pK_{a_base} - pH_{Caco2})})}{(1 + 10^{(pH_{lum33} - pK_{a_acid})} + 10^{(pK_{a_base} - pH_{lum33})})}$,
 $PS_{pass_a33} = P_{invivo} ME_{Sent33}$,

$PS_{pass_b33} = P_{invivo} Sent33,$
 $PS_{pass_lum_a33} = P_{pass_lum_a33} ME Sent33,$
 $PS_{ap33} = PS_{pass_lum_a33},$
 $PS_{bp33} = PS_{pass_b33},$
 $PS_{bx33} = PS_{pass_b33},$
 $PS_{pgp33} = \frac{psf_Pgp V_{max_Pgp} A_{rel_Pgp33}}{(K_{m_Pgp} + fent y_{133}/Vent33)},$
 $PS_{ax33} = (PS_{pass_a33} + PS_{pgp33}),$
 $CL33 = \frac{V_{max_3A4} A_{rel_3A4_33}}{(K_{m_3A4} + fent y_{133}/Vent33) / (1 + (fent_inh * y_{263}/Vent33) / K_{i_3A4})},$

$P_{pass_lum_a34} = P_{invivo} \frac{(1 + 10^{(pH_Caco2 - pK_{a_acid})}) + 10^{(pK_{a_base} - pH_Caco2)}}{(1 + 10^{(pH_lum34 - pK_{a_acid})}) + 10^{(pK_{a_base} - pH_lum34)}},$
 $PS_{pass_a34} = P_{invivo} ME Sent34,$
 $PS_{pass_b34} = P_{invivo} Sent34,$
 $PS_{pass_lum_a34} = P_{pass_lum_a34} ME Sent34,$
 $PS_{ap34} = PS_{pass_lum_a34},$
 $PS_{bp34} = PS_{pass_b34},$
 $PS_{bx34} = PS_{pass_b34},$
 $PS_{pgp34} = \frac{psf_Pgp V_{max_Pgp} A_{rel_Pgp34}}{(K_{m_Pgp} + fent y_{134}/Vent34)},$
 $PS_{ax34} = (PS_{pass_a34} + PS_{pgp34}),$
 $CL34 = \frac{V_{max_3A4} A_{rel_3A4_34}}{(K_{m_3A4} + fent y_{134}/Vent34) / (1 + (fent_inh * y_{264}/Vent34) / K_{i_3A4})},$

$P_{pass_lum_a35} = P_{invivo} \frac{(1 + 10^{(pH_Caco2 - pK_{a_acid})}) + 10^{(pK_{a_base} - pH_Caco2)}}{(1 + 10^{(pH_lum35 - pK_{a_acid})}) + 10^{(pK_{a_base} - pH_lum35)}},$

$$PS_{pass_a35} = P_{invivo} ME_{Sent35},$$

$$PS_{pass_b35} = P_{invivo} Sent35,$$

$$PS_{pass_lum_a35} = P_{pass_lum_a35} ME_{Sent35},$$

$$PS_{ap35} = PS_{pass_lum_a35},$$

$$PS_{bp35} = PS_{pass_b35},$$

$$PS_{bx35} = PS_{pass_b35},$$

$$PS_{pgp35} = \frac{psf_Pgp \cdot V_{max_Pgp} \cdot A_{rel_Pgp35}}{(K_{m_Pgp} + f_{ent} \cdot y_{135}/V_{ent35})},$$

$$PS_{ax35} = (PS_{pass_a35} + PS_{pgp35}),$$

$$CL_{35} = \frac{V_{max_3A4} \cdot A_{rel_3A4_35}}{(K_{m_3A4} + f_{ent} \cdot y_{135}/V_{ent35}) / (1 + (f_{ent_inh} \cdot y_{265}/V_{ent35}) / K_{i_3A4})},$$

$$P_{pass_lum_a36} = P_{invivo} \frac{(1 + 10^{(pH_{Caco2} - pK_{a_acid})}) + 10^{(pK_{a_base} - pH_{Caco2})}}{(1 + 10^{(pH_{lum36} - pK_{a_acid})}) + 10^{(pK_{a_base} - pH_{lum36})}},$$

$$PS_{pass_a36} = P_{invivo} ME_{Sent36},$$

$$PS_{pass_b36} = P_{invivo} Sent36,$$

$$PS_{pass_lum_a36} = P_{pass_lum_a36} ME_{Sent36},$$

$$PS_{ap36} = PS_{pass_lum_a36},$$

$$PS_{bp36} = PS_{pass_b36},$$

$$PS_{bx36} = PS_{pass_b36},$$

$$PS_{pgp36} = \frac{psf_Pgp \cdot V_{max_Pgp} \cdot A_{rel_Pgp36}}{(K_{m_Pgp} + f_{ent} \cdot y_{136}/V_{ent36})},$$

$$PS_{ax36} = (PS_{pass_a36} + PS_{pgp36}),$$

$$CL_{36} = \frac{V_{max_3A4} \cdot A_{rel_3A4_36}}{(K_{m_3A4} + f_{ent} \cdot y_{136}/V_{ent36}) / (1 + (f_{ent_inh} \cdot y_{266}/V_{ent36}) / K_{i_3A4})},$$

$$P_{\text{pass_lum_a37}} = P_{\text{invivo}} \frac{(1+10^{(\text{pH_Caco2}-\text{pKa_acid})}+10^{(\text{pKa_base}-\text{pH_Caco2}))}}{(1+10^{(\text{pH_lum37}-\text{pKa_acid})}+10^{(\text{pKa_base}-\text{pH_lum37}))},$$

$$P_{\text{Spass_a37}} = P_{\text{invivo}} \text{ME Sent37},$$

$$P_{\text{Spass_b37}} = P_{\text{invivo}} \text{Sent37},$$

$$P_{\text{Spass_lum_a37}} = P_{\text{pass_lum_a37}} \text{ME Sent37},$$

$$P_{\text{Sap37}} = P_{\text{Spass_lum_a37}},$$

$$P_{\text{Sbp37}} = P_{\text{Spass_b37}},$$

$$P_{\text{Sbx37}} = P_{\text{Spass_b37}},$$

$$P_{\text{Spgp37}} = \text{psf_Pgp} \frac{V_{\text{max_Pgp}} \text{Arel_Pgp37}}{(K_{\text{m_Pgp}} + \text{fent y137/Vent37})},$$

$$P_{\text{Sax37}} = (P_{\text{Spass_a37}} + P_{\text{Spgp37}}),$$

$$CL_{37} = \frac{V_{\text{max_3A4}} \text{Arel_3A4_37}}{(K_{\text{m_3A4}} + \text{fent y137/Vent37})} \frac{1}{(1 + (\text{fent_inh} * \text{y267/Vent37}) / K_{\text{i_3A4}})},$$

$$P_{\text{pass_lum_a38}} = P_{\text{invivo}} \frac{(1+10^{(\text{pH_Caco2}-\text{pKa_acid})}+10^{(\text{pKa_base}-\text{pH_Caco2}))}}{(1+10^{(\text{pH_lum38}-\text{pKa_acid})}+10^{(\text{pKa_base}-\text{pH_lum38}))},$$

$$P_{\text{Spass_a38}} = P_{\text{invivo}} \text{ME Sent38},$$

$$P_{\text{Spass_b38}} = P_{\text{invivo}} \text{Sent38},$$

$$P_{\text{Spass_lum_a38}} = P_{\text{pass_lum_a38}} \text{ME Sent38},$$

$$P_{\text{Sap38}} = P_{\text{Spass_lum_a38}},$$

$$P_{\text{Sbp38}} = P_{\text{Spass_b38}},$$

$$P_{\text{Sbx38}} = P_{\text{Spass_b38}},$$

$$P_{\text{Spgp38}} = \text{psf_Pgp} \frac{V_{\text{max_Pgp}} \text{Arel_Pgp38}}{(K_{\text{m_Pgp}} + \text{fent y138/Vent38})},$$

$$P_{\text{Sax38}} = (P_{\text{Spass_a38}} + P_{\text{Spgp38}}),$$

$$CL_{38} = \frac{V_{\text{max_3A4}} \text{Arel_3A4_38}}{(K_{\text{m_3A4}} + \text{fent y138/Vent38})} \frac{1}{(1 + (\text{fent_inh} * \text{y268/Vent38}) / K_{\text{i_3A4}})},$$

$$P_{\text{pass_lum_a39}} = P_{\text{invivo}} \frac{(1+10^{(\text{pH_Caco2}-\text{pKa_acid})}+10^{(\text{pKa_base}-\text{pH_Caco2})})}{(1+10^{(\text{pH_lum39}-\text{pKa_acid})}+10^{(\text{pKa_base}-\text{pH_lum39})})},$$

$$P_{\text{Spass_a39}} = P_{\text{invivo}} \text{ME Sent39},$$

$$P_{\text{Spass_b39}} = P_{\text{invivo}} \text{Sent39},$$

$$P_{\text{Spass_lum_a39}} = P_{\text{pass_lum_a39}} \text{ME Sent39},$$

$$P_{\text{Sap39}} = P_{\text{Spass_lum_a39}},$$

$$P_{\text{Sbp39}} = P_{\text{Spass_b39}},$$

$$P_{\text{Sbx39}} = P_{\text{Spass_b39}},$$

$$P_{\text{Spgp39}} = \text{psf_Pgp} \frac{V_{\text{max_Pgp}} \text{Arel_Pgp39}}{(K_{\text{m_Pgp}} + \text{fent y139/Vent39})},$$

$$P_{\text{Sax39}} = (P_{\text{Spass_a39}} + P_{\text{Spgp39}}),$$

$$CL_{39} = \frac{V_{\text{max_3A4}} \text{Arel_3A4_39}}{(K_{\text{m_3A4}} + \text{fent y139/Vent39}) / (1 + (\text{fent_inh} * \text{y269/Vent39}) / K_{\text{i_3A4}})},$$

$$P_{\text{pass_lum_a40}} = P_{\text{invivo}} \frac{(1+10^{(\text{pH_Caco2}-\text{pKa_acid})}+10^{(\text{pKa_base}-\text{pH_Caco2})})}{(1+10^{(\text{pH_lum40}-\text{pKa_acid})}+10^{(\text{pKa_base}-\text{pH_lum40})})},$$

$$P_{\text{Spass_a40}} = P_{\text{invivo}} \text{ME Sent40},$$

$$P_{\text{Spass_b40}} = P_{\text{invivo}} \text{Sent40},$$

$$P_{\text{Spass_lum_a40}} = P_{\text{pass_lum_a40}} \text{ME Sent40},$$

$$P_{\text{Sap40}} = P_{\text{Spass_lum_a40}},$$

$$P_{\text{Sbp40}} = P_{\text{Spass_b40}},$$

$$P_{\text{Sbx40}} = P_{\text{Spass_b40}},$$

$$P_{\text{Spgp40}} = \text{psf_Pgp} \frac{V_{\text{max_Pgp}} \text{Arel_Pgp40}}{(K_{\text{m_Pgp}} + \text{fent y140/Vent40})},$$

$$P_{\text{Sax40}} = (P_{\text{Spass_a40}} + P_{\text{Spgp40}}),$$

$$CL40 = \frac{V_{max_3A4} A_{rel_3A4_40}}{(K_m_3A4 + f_{ent} y_{140} / V_{ent40}) (1 + (f_{ent_inh} y_{270} / V_{ent40}) / K_i_3A4)},$$

; Water volume in the small intestine at each location (substrate)

$$y_1' = (kg * y_{43}) V_g \text{ div} / V + (c_{3a_1} - k_{w_1}) * y_1 + c_{4a_2} * y_2 + c_{5_3} * y_3 + sw_1,$$

$$y_2' = c_{2a_1} * y_1 + c_{3_2_kw} * y_2 + c_{4_3} * y_3 + c_{5_4} * y_4 + sw_2,$$

$$y_3' = c_{1_1} * y_1 + c_{2_2} * y_2 + c_{3_3_kw} * y_3 + c_{4_4} * y_4 + c_{5_5} * y_5 + sw_3,$$

$$y_4' = c_{1_2} * y_2 + c_{2_3} * y_3 + c_{3_4_kw} * y_4 + c_{4_5} * y_5 + c_{5_6} * y_6 + sw_4,$$

$$y_5' = c_{1_3} * y_3 + c_{2_4} * y_4 + c_{3_5_kw} * y_5 + c_{4_6} * y_6 + c_{5_7} * y_7 + sw_5,$$

$$y_6' = c_{1_4} * y_4 + c_{2_5} * y_5 + c_{3_6_kw} * y_6 + c_{4_7} * y_7 + c_{5_8} * y_8 + sw_6,$$

$$y_7' = c_{1_5} * y_5 + c_{2_6} * y_6 + c_{3_7_kw} * y_7 + c_{4_8} * y_8 + c_{5_9} * y_9 + sw_7,$$

$$y_8' = c_{1_6} * y_6 + c_{2_7} * y_7 + c_{3_8_kw} * y_8 + c_{4_9} * y_9 + c_{5_10} * y_{10} + sw_8,$$

$$y_9' = c_{1_7} * y_7 + c_{2_8} * y_8 + c_{3_9_kw} * y_9 + c_{4_10} * y_{10} + c_{5_11} * y_{11} + sw_9,$$

$$y_{10}' = c_{1_8} * y_8 + c_{2_9} * y_9 + c_{3_10_kw} * y_{10} + c_{4_11} * y_{11} + c_{5_12} * y_{12} + sw_{10},$$

$$y_{11}' = c_{1_9} * y_9 + c_{2_10} * y_{10} + c_{3_11_kw} * y_{11} + c_{4_12} * y_{12} + c_{5_13} * y_{13} + sw_{11},$$

$$y_{12}' = c_{1_10} * y_{10} + c_{2_11} * y_{11} + c_{3_12_kw} * y_{12} + c_{4_13} * y_{13} + c_{5_14} * y_{14} + sw_{12},$$

$$y_{13}' = c_{1_11} * y_{11} + c_{2_12} * y_{12} + c_{3_13_kw} * y_{13} + c_{4_14} * y_{14} + c_{5_15} * y_{15} + sw_{13},$$

$$y_{14}' = c_{1_12} * y_{12} + c_{2_13} * y_{13} + c_{3_14_kw} * y_{14} + c_{4_15} * y_{15} + c_{5_16} * y_{16} + sw_{14},$$

$$y_{15}' = c_{1_13} * y_{13} + c_{2_14} * y_{14} + c_{3_15_kw} * y_{15} + c_{4_16} * y_{16} + c_{5_17} * y_{17} + sw_{15},$$

$$y_{16}' = c_{1_14} * y_{14} + c_{2_15} * y_{15} + c_{3_16_kw} * y_{16} + c_{4_17} * y_{17} + c_{5_18} * y_{18} + sw_{16},$$

$$y_{17}' = c_{1_15} * y_{15} + c_{2_16} * y_{16} + c_{3_17_kw} * y_{17} + c_{4_18} * y_{18} + c_{5_19} * y_{19} + sw_{17},$$

$$y_{18}' = c_{1_16} * y_{16} + c_{2_17} * y_{17} + c_{3_18_kw} * y_{18} + c_{4_19} * y_{19} + c_{5_20} * y_{20} + sw_{18},$$

$$y_{19}' = c_{1_17} * y_{17} + c_{2_18} * y_{18} + c_{3_19_kw} * y_{19} + c_{4_20} * y_{20} + c_{5_21} * y_{21} + sw_{19},$$

$$y_{20}' = c_{1_18} * y_{18} + c_{2_19} * y_{19} + c_{3_20_kw} * y_{20} + c_{4_21} * y_{21} + c_{5_22} * y_{22} + sw_{20},$$

$$y_{21}' = c_{1_19} * y_{19} + c_{2_20} * y_{20} + c_{3_21_kw} * y_{21} + c_{4_22} * y_{22} + c_{5_23} * y_{23} + sw_{21},$$

$$\begin{aligned}
y_{22}' &= c1_{20}*y_{20} + c2_{21}*y_{21} + c3_{22_kw}*y_{22} + c4_{23}*y_{23} + c5_{24}*y_{24}+sw_{22}, \\
y_{23}' &= c1_{21}*y_{21} + c2_{22}*y_{22} + c3_{23_kw}*y_{23} + c4_{24}*y_{24} + c5_{25}*y_{25}+sw_{23}, \\
y_{24}' &= c1_{22}*y_{22} + c2_{23}*y_{23} + c3_{24_kw}*y_{24} + c4_{25}*y_{25} + c5_{26}*y_{26}+sw_{24}, \\
y_{25}' &= c1_{23}*y_{23} + c2_{24}*y_{24} + c3_{25_kw}*y_{25} + c4_{26}*y_{26} + c5_{27}*y_{27}+sw_{25}, \\
y_{26}' &= c1_{24}*y_{24} + c2_{25}*y_{25} + c3_{26_kw}*y_{26} + c4_{27}*y_{27} + c5_{28}*y_{28}+sw_{26}, \\
y_{27}' &= c1_{25}*y_{25} + c2_{26}*y_{26} + c3_{27_kw}*y_{27} + c4_{28}*y_{28} + c5_{29}*y_{29}+sw_{27}, \\
y_{28}' &= c1_{26}*y_{26} + c2_{27}*y_{27} + c3_{28_kw}*y_{28} + c4_{29}*y_{29} + c5_{30}*y_{30}+sw_{28}, \\
y_{29}' &= c1_{27}*y_{27} + c2_{28}*y_{28} + c3_{29_kw}*y_{29} + c4_{30}*y_{30} + c5_{31}*y_{31}+sw_{29}, \\
y_{30}' &= c1_{28}*y_{28} + c2_{29}*y_{29} + c3_{30_kw}*y_{30} + c4_{31}*y_{31} + c5_{32}*y_{32}+sw_{30}, \\
y_{31}' &= c1_{29}*y_{29} + c2_{30}*y_{30} + c3_{31_kw}*y_{31} + c4_{32}*y_{32} + c5_{33}*y_{33}+sw_{31}, \\
y_{32}' &= c1_{30}*y_{30} + c2_{31}*y_{31} + c3_{32_kw}*y_{32} + c4_{33}*y_{33} + c5_{34}*y_{34}+sw_{32}, \\
y_{33}' &= c1_{31}*y_{31} + c2_{32}*y_{32} + c3_{33_kw}*y_{33} + c4_{34}*y_{34} + c5_{35}*y_{35}+sw_{33}, \\
y_{34}' &= c1_{32}*y_{32} + c2_{33}*y_{33} + c3_{34_kw}*y_{34} + c4_{35}*y_{35} + c5_{36}*y_{36}+sw_{34}, \\
y_{35}' &= c1_{33}*y_{33} + c2_{34}*y_{34} + c3_{35_kw}*y_{35} + c4_{36}*y_{36} + c5_{37}*y_{37}+sw_{35}, \\
y_{36}' &= c1_{34}*y_{34} + c2_{35}*y_{35} + c3_{36_kw}*y_{36} + c4_{37}*y_{37} + c5_{38}*y_{38}+sw_{36}, \\
y_{37}' &= c1_{35}*y_{35} + c2_{36}*y_{36} + c3_{37_kw}*y_{37} + c4_{38}*y_{38} + c5_{39}*y_{39}+sw_{37}, \\
y_{38}' &= c1_{36}*y_{36} + c2_{37}*y_{37} + c3_{38_kw}*y_{38} + c4_{39}*y_{39} + c5_{40}*y_{40}+sw_{38}, \\
y_{39}' &= c1_{37}*y_{37} + c2_{38}*y_{38} + c3_{39_kw}*y_{39} + c4a_{40}*y_{40}+sw_{39}, \\
y_{40}' &= c1_{38}*y_{38} + c2b_{39}*y_{39} + (c3b_{40}-kw_{40})*y_{40}+sw_{40},
\end{aligned}$$

; Water volume in the caecum/colon

$$y_{41}' = ((9.0 y_{40} - y_{39}) / 8.0) Q - (kw_{col}+krec) * y_{41}+sw_{col},$$

; Water volume in feces (assumed to be 0)

$$y_{42}' = krec*y_{41},$$

; Water volume in stomach

$$y_{43}' = k_a * y_{50} - (k_g + k_{w_gut}) * y_{43} + s_{w_gut},$$

; Water volume in the upper small intestine (not used in this study)

$$y_{44} = (y_1 + y_2 + y_3 + y_4 + y_5 + y_6 + y_7 + y_8 + y_9 + y_{10} + y_{11} + y_{12} + y_{13} + y_{14} + y_{15} + y_{16} + y_{17} + y_{18} + y_{19} + y_{20} + y_{21} + y_{22} + y_{23} + y_{24}),$$

; Water volume in the lower small intestine (not used in this study)

$$y_{45} = (y_{25} + y_{26} + y_{27} + y_{28} + y_{29} + y_{30} + y_{31} + y_{32} + y_{33} + y_{34} + y_{35} + y_{36} + y_{37} + y_{38} + y_{39} + y_{40}),$$

; Water volume in the whole small intestine

$$y_{46} =$$

$$y_1 + y_2 + y_3 + y_4 + y_5 + y_6 + y_7 + y_8 + y_9 + y_{10} + y_{11} + y_{12} + y_{13} + y_{14} + y_{15} + y_{16} + y_{17} + y_{18} + y_{19} + y_{20} + y_{21} + y_{22} + y_{23} + y_{24} + y_{25} + y_{26} + y_{27} + y_{28} + y_{29} + y_{30} + y_{31} + y_{32} + y_{33} + y_{34} + y_{35} + y_{36} + y_{37} + y_{38} + y_{39} + y_{40},$$

; Water volume in distal jejunum and proximal ileum (not used in this study)

$$y_{48} =$$

$$(y_{12} + y_{13} + y_{14} + y_{15} + y_{16} + y_{17} + y_{18} + y_{19} + y_{20} + y_{21} + y_{22} + y_{23} + y_{24} + y_{25} + y_{26} + y_{27} + y_{28} + y_{29} + y_{30}),$$

; Water volume in distal ileum (not used in this study)

$$y_{49} = (y_{31} + y_{32} + y_{33} + y_{34} + y_{35} + y_{36} + y_{37} + y_{38} + y_{39} + y_{40}),$$

; Water volume in the esophagus)

$$y50' = -ka*y50,$$

; Following is the codes about a substrate

; Drug concentration in the small intestine

$$y51' = (kg * y93) * Vg \text{ div} / V + c3a_1*y51 + c4a_2*y52 + c5_3*y53 -$$

$$PSap1*y51/y1+PSax1*fent*y101/Vent1/(V/div),$$

if y51 < 0 then y51=0 endif,

$$y52' = c2a_1*y51 + c3_2*y52 + c4_3*y53 + c5_4*y54 -$$

$$PSap2*y52/y2+PSax2*fent*y102/Vent2/(V/div),$$

if y52 < 0 then y52=0 endif,

$$y53' = c1_1*y51 + c2_2*y52 + c3_3*y53 + c4_4*y54 + c5_5*y55 -$$

$$PSap3*y53/y3+PSax3*fent*y103/Vent3/(V/div),$$

if y53 < 0 then y53=0 endif,

$$y54' = c1_2*y52 + c2_3*y53 + c3_4*y54 + c4_5*y55 + c5_6*y56 -$$

$$PSap4*y54/y4+PSax4*fent*y104/Vent4/(V/div),$$

if y54 < 0 then y54=0 endif,

$$y55' = c1_3*y53 + c2_4*y54 + c3_5*y55 + c4_6*y56 + c5_7*y57 -$$

$$PSap5*y55/y5+PSax5*fent*y105/Vent5/(V/div),$$

if y55 < 0 then y55=0 endif,

$$y56' = c1_4*y54 + c2_5*y55 + c3_6*y56 + c4_7*y57 + c5_8*y58 -$$

$$PSap6*y56/y6+PSax6*fent*y106/Vent6/(V/div),$$

if y56 < 0 then y56=0 endif,

$$y57' = c1_5*y55 + c2_6*y56 + c3_7*y57 + c4_8*y58 + c5_9*y59 -$$

$$PSap7*y57/y7+PSax7*fent*y107/Vent7/(V/div),$$

if y57 < 0 then y57=0 endif,

$$y58' = c1_6*y56 + c2_7*y57 + c3_8*y58 + c4_9*y59 + c5_10*y60 -$$

$$PSap8*y58/y8 + PSax8*fent*y108/Vent8/(V/div),$$

if y58 < 0 then y58=0 endif,

$$y59' = c1_7*y57 + c2_8*y58 + c3_9*y59 + c4_10*y60 + c5_11*y61 -$$

$$PSap9*y59/y9 + PSax9*fent*y109/Vent9/(V/div),$$

if y59 < 0 then y59=0 endif,

$$y60' = c1_8*y58 + c2_9*y59 + c3_10*y60 + c4_11*y61 + c5_12*y62 -$$

$$PSap10*y60/y10 + PSax10*fent*y110/Vent10/(V/div),$$

if y60 < 0 then y60=0 endif,

$$y61' = c1_9*y59 + c2_10*y60 + c3_11*y61 + c4_12*y62 + c5_13*y63 -$$

$$PSap11*y61/y11 + PSax11*fent*y111/Vent11/(V/div),$$

if y61 < 0 then y61=0 endif,

$$y62' = c1_10*y60 + c2_11*y61 + c3_12*y62 + c4_13*y63 + c5_14*y64 -$$

$$PSap12*y62/y12 + PSax12*fent*y112/Vent12/(V/div),$$

if y62 < 0 then y62=0 endif,

$$y63' = c1_11*y61 + c2_12*y62 + c3_13*y63 + c4_14*y64 + c5_15*y65 -$$

$$PSap13*y63/y13 + PSax13*fent*y113/Vent13/(V/div),$$

if y63 < 0 then y63=0 endif,

$$y64' = c1_12*y62 + c2_13*y63 + c3_14*y64 + c4_15*y65 + c5_16*y66 -$$

$$PSap14*y64/y14 + PSax14*fent*y114/Vent14/(V/div),$$

if y64 < 0 then y64=0 endif,

$$y65' = c1_13*y63 + c2_14*y64 + c3_15*y65 + c4_16*y66 + c5_17*y67 -$$

$$PSap15*y65/y15 + PSax15*fent*y115/Vent15/(V/div),$$

if y65 < 0 then y65=0 endif,

$$y66' = c1_{14}*y64 + c2_{15}*y65 + c3_{16}*y66 + c4_{17}*y67 + c5_{18}*y68 -$$

$$PSap16*y66/y16+PSax16*fent*y116/Vent16/(V/div),$$

if y66 < 0 then y66=0 endif,

$$y67' = c1_{15}*y65 + c2_{16}*y66 + c3_{17}*y67 + c4_{18}*y68 + c5_{19}*y69 -$$

$$PSap17*y67/y17+PSax17*fent*y117/Vent17/(V/div),$$

if y67 < 0 then y67=0 endif,

$$y68' = c1_{16}*y66 + c2_{17}*y67 + c3_{18}*y68 + c4_{19}*y69 + c5_{20}*y70 -$$

$$PSap18*y68/y18+PSax18*fent*y118/Vent18/(V/div),$$

if y68 < 0 then y68=0 endif,

$$y69' = c1_{17}*y67 + c2_{18}*y68 + c3_{19}*y69 + c4_{20}*y70 + c5_{21}*y71 -$$

$$PSap19*y69/y19+PSax19*fent*y119/Vent19/(V/div),$$

if y69 < 0 then y69=0 endif,

$$y70' = c1_{18}*y68 + c2_{19}*y69 + c3_{20}*y70 + c4_{21}*y71 + c5_{22}*y72 -$$

$$PSap20*y70/y20+PSax20*fent*y120/Vent20/(V/div),$$

if y70 < 0 then y70=0 endif,

$$y71' = c1_{19}*y69 + c2_{20}*y70 + c3_{21}*y71 + c4_{22}*y72 + c5_{23}*y73 -$$

$$PSap21*y71/y21+PSax21*fent*y121/Vent21/(V/div),$$

if y71 < 0 then y71=0 endif,

$$y72' = c1_{20}*y70 + c2_{21}*y71 + c3_{22}*y72 + c4_{23}*y73 + c5_{24}*y74 -$$

$$PSap22*y72/y22+PSax22*fent*y122/Vent22/(V/div),$$

if y72 < 0 then y72=0 endif,

$$y73' = c1_{21}*y71 + c2_{22}*y72 + c3_{23}*y73 + c4_{24}*y74 + c5_{25}*y75 -$$

$$PSap23*y73/y23+PSax23*fent*y123/Vent23/(V/div),$$

if y73 < 0 then y73=0 endif,

$$y74' = c1_22*y72 + c2_23*y73 + c3_24*y74 + c4_25*y75 + c5_26*y76 -$$

$$PSap24*y74/y24 + PSax24*fent*y124/Vent24/(V/div),$$

if y74 < 0 then y74=0 endif,

$$y75' = c1_23*y73 + c2_24*y74 + c3_25*y75 + c4_26*y76 + c5_27*y77 -$$

$$PSap25*y75/y25 + PSax25*fent*y125/Vent25/(V/div),$$

if y75 < 0 then y75=0 endif,

$$y76' = c1_24*y74 + c2_25*y75 + c3_26*y76 + c4_27*y77 + c5_28*y78 -$$

$$PSap26*y76/y26 + PSax26*fent*y126/Vent26/(V/div),$$

if y76 < 0 then y76=0 endif,

$$y77' = c1_25*y75 + c2_26*y76 + c3_27*y77 + c4_28*y78 + c5_29*y79 -$$

$$PSap27*y77/y27 + PSax27*fent*y127/Vent27/(V/div),$$

if y77 < 0 then y77=0 endif,

$$y78' = c1_26*y76 + c2_27*y77 + c3_28*y78 + c4_29*y79 + c5_30*y80 -$$

$$PSap28*y78/y28 + PSax28*fent*y128/Vent28/(V/div),$$

if y78 < 0 then y78=0 endif,

$$y79' = c1_27*y77 + c2_28*y78 + c3_29*y79 + c4_30*y80 + c5_31*y81 -$$

$$PSap29*y79/y29 + PSax29*fent*y129/Vent29/(V/div),$$

if y79 < 0 then y79=0 endif,

$$y80' = c1_28*y78 + c2_29*y79 + c3_30*y80 + c4_31*y81 + c5_32*y82 -$$

$$PSap30*y80/y30 + PSax30*fent*y130/Vent30/(V/div),$$

if y80 < 0 then y80=0 endif,

$$y81' = c1_29*y79 + c2_30*y80 + c3_31*y81 + c4_32*y82 + c5_33*y83 -$$

$$PSap31*y81/y31 + PSax31*fent*y131/Vent31/(V/div),$$

if y81 < 0 then y81=0 endif,

$$y_{82}' = c_{1_30} * y_{80} + c_{2_31} * y_{81} + c_{3_32} * y_{82} + c_{4_33} * y_{83} + c_{5_34} * y_{84} -$$

$$PSap_{32} * y_{82} / y_{32} + PSax_{32} * fent * y_{132} / Vent_{32} / (V / div),$$

if $y_{82} < 0$ then $y_{82} = 0$ endif,

$$y_{83}' = c_{1_31} * y_{81} + c_{2_32} * y_{82} + c_{3_33} * y_{83} + c_{4_34} * y_{84} + c_{5_35} * y_{85} -$$

$$PSap_{33} * y_{83} / y_{33} + PSax_{33} * fent * y_{133} / Vent_{33} / (V / div),$$

if $y_{83} < 0$ then $y_{83} = 0$ endif,

$$y_{84}' = c_{1_32} * y_{82} + c_{2_33} * y_{83} + c_{3_34} * y_{84} + c_{4_35} * y_{85} + c_{5_36} * y_{86} -$$

$$PSap_{34} * y_{84} / y_{34} + PSax_{34} * fent * y_{134} / Vent_{34} / (V / div),$$

if $y_{84} < 0$ then $y_{84} = 0$ endif,

$$y_{85}' = c_{1_33} * y_{83} + c_{2_34} * y_{84} + c_{3_35} * y_{85} + c_{4_36} * y_{86} + c_{5_37} * y_{87} -$$

$$PSap_{35} * y_{85} / y_{35} + PSax_{35} * fent * y_{135} / Vent_{35} / (V / div),$$

if $y_{85} < 0$ then $y_{85} = 0$ endif,

$$y_{86}' = c_{1_34} * y_{84} + c_{2_35} * y_{85} + c_{3_36} * y_{86} + c_{4_37} * y_{87} + c_{5_38} * y_{88} -$$

$$PSap_{36} * y_{86} / y_{36} + PSax_{36} * fent * y_{136} / Vent_{36} / (V / div),$$

if $y_{86} < 0$ then $y_{86} = 0$ endif,

$$y_{87}' = c_{1_35} * y_{85} + c_{2_36} * y_{86} + c_{3_37} * y_{87} + c_{4_38} * y_{88} + c_{5_39} * y_{89} -$$

$$PSap_{37} * y_{87} / y_{37} + PSax_{37} * fent * y_{137} / Vent_{37} / (V / div),$$

if $y_{87} < 0$ then $y_{87} = 0$ endif,

$$y_{88}' = c_{1_36} * y_{86} + c_{2_37} * y_{87} + c_{3_38} * y_{88} + c_{4_39} * y_{89} + c_{5_40} * y_{90} -$$

$$PSap_{38} * y_{88} / y_{38} + PSax_{38} * fent * y_{138} / Vent_{38} / (V / div),$$

if $y_{88} < 0$ then $y_{88} = 0$ endif,

$$y_{89}' = c_{1_37} * y_{87} + c_{2_38} * y_{88} + c_{3_39} * y_{89} + c_{4a_40} * y_{90} -$$

$$PSap_{39} * y_{89} / y_{39} + PSax_{39} * fent * y_{139} / Vent_{39} / (V / div),$$

if $y_{89} < 0$ then $y_{89} = 0$ endif,

$$y90' = c1_{38} * y88 + c2b_{39} * y89 + c3b_{40} * y90 -$$

$$PSap40 * y90 / y40 + PSax40 * fent * y140 / Vent40 / (V / div),$$

if $y90 < 0$ then $y90 = 0$ endif,

; Drug amount in the colon

$$y91' = ((9.0 y90 - y89) / 8.0) Q - krec * y91,$$

; Drug amount in the feces

$$y92' = krec * y91 * Vcaecol,$$

; Drug concentration in the stomach

$$y93' = ka * y100 * Ves / Vg - kg * y93,$$

; % of dose in stomach (used in the analysis of ^{99m}Tc -DTPA)

$$y94 = y93 Vg / dose * 100,$$

; % of dose in jejunum (used in the analysis of ^{99m}Tc -DTPA)

$$y95 = (y51 + y52 + y53 + y54 + y55 + y56 + y57 + y58 + y59 + y60 + y61 + y62 + y63 + y64 + y65 + y66 + y67 + y68 + y69 + y70) V / div / dose * 100,$$

; % of dose in ileum (used in the analysis of ^{99m}Tc -DTPA)

$$y96 = (y71 + y72 + y73 + y74 + y75 + y76 + y77 + y78 + y79 + y80 + y81 + y82 + y83 + y84 + y85 + y86 + y87 + y88 + y89 + y90) V / div / dose * 100,$$

; % of dose in colon (used in the analysis of ^{99m}Tc -DTPA)

$$y97 = y91 Vc / dose * 100,$$

; % of dose in whole lumen (not used in this study)

$$y98 = y95 + y96 + y97,$$

; Drug amount in the gastrointestinal tract (not used in this study)

$$y99 = y94 + y95 + y96 + y97,$$

; Drug concentration in the esophagus

$$y100' = -ka * y100,$$

; Drug amount in the enterocytes

$$y101' = PSap1 * y51 * (V/div) / y1 - (PSax1 + CL1 + PSbp1) * fent * y101 / Vent1 + PSbx1 * y141 / Vlam1,$$

if y101 < 0 then y101=0 endif,

$$y102' = PSap2 * y52 * (V/div) / y2 - (PSax2 + CL2 + PSbp2) * fent * y102 / Vent2 + PSbx2 * y142 / Vlam2,$$

if y102 < 0 then y102=0 endif,

$$y103' = PSap3 * y53 * (V/div) / y3 - (PSax3 + CL3 + PSbp3) * fent * y103 / Vent3 + PSbx3 * y143 / Vlam3,$$

if y103 < 0 then y103=0 endif,

$$y104' = PSap4 * y54 * (V/div) / y4 - (PSax4 + CL4 + PSbp4) * fent * y104 / Vent4 + PSbx4 * y144 / Vlam4,$$

if y104 < 0 then y104=0 endif,

$$y105' = PSap5 * y55 * (V/div) / y5 - (PSax5 + CL5 + PSbp5) * fent * y105 / Vent5 + PSbx5 * y145 / Vlam5,$$

if y105 < 0 then y105=0 endif,

$$y106' = PSap6 * y56 * (V/div) / y6 - (PSax6 + CL6 + PSbp6) * fent * y106 / Vent6 + PSbx6 * y146 / Vlam6,$$

if y106 < 0 then y106=0 endif,

$$y107' = PSap7 * y57 * (V/div) / y7 - (PSax7 + CL7 + PSbp7) * fent * y107 / Vent7 + PSbx7 * y147 / Vlam7,$$

if $y_{107} < 0$ then $y_{107}=0$ endif,
 $y_{108}'=PSap8*y_{58}*(V/div)/y_8-(PSax8+CL8+PSbp8)*fent*y_{108}/Vent8+PSbx8*y_{148}/Vlam8,$
 if $y_{108} < 0$ then $y_{108}=0$ endif,
 $y_{109}'=PSap9*y_{59}*(V/div)/y_9-(PSax9+CL9+PSbp9)*fent*y_{109}/Vent9+PSbx9*y_{149}/Vlam9,$
 if $y_{109} < 0$ then $y_{109}=0$ endif,
 $y_{110}'=PSap10*y_{60}*(V/div)/y_{10}-$
 $(PSax10+CL10+PSbp10)*fent*y_{110}/Vent10+PSbx10*y_{150}/Vlam10,$
 if $y_{110} < 0$ then $y_{110}=0$ endif,
 $y_{111}'=PSap11*y_{61}*(V/div)/y_{11}-$
 $(PSax11+CL11+PSbp11)*fent*y_{111}/Vent11+PSbx11*y_{151}/Vlam11,$
 if $y_{111} < 0$ then $y_{111}=0$ endif,
 $y_{112}'=PSap12*y_{62}*(V/div)/y_{12}-$
 $(PSax12+CL12+PSbp12)*fent*y_{112}/Vent12+PSbx12*y_{152}/Vlam12,$
 if $y_{112} < 0$ then $y_{112}=0$ endif,
 $y_{113}'=PSap13*y_{63}*(V/div)/y_{13}-$
 $(PSax13+CL13+PSbp13)*fent*y_{113}/Vent13+PSbx13*y_{153}/Vlam13,$
 if $y_{113} < 0$ then $y_{113}=0$ endif,
 $y_{114}'=PSap14*y_{64}*(V/div)/y_{14}-$
 $(PSax14+CL14+PSbp14)*fent*y_{114}/Vent14+PSbx14*y_{154}/Vlam14,$
 if $y_{114} < 0$ then $y_{114}=0$ endif,
 $y_{115}'=PSap15*y_{65}*(V/div)/y_{15}-$
 $(PSax15+CL15+PSbp15)*fent*y_{115}/Vent15+PSbx15*y_{155}/Vlam15,$
 if $y_{115} < 0$ then $y_{115}=0$ endif,
 $y_{116}'=PSap16*y_{66}*(V/div)/y_{16}-$
 $(PSax16+CL16+PSbp16)*fent*y_{116}/Vent16+PSbx16*y_{156}/Vlam16,$

if $y_{116} < 0$ then $y_{116}=0$ endif,
 $y_{117}'=PS_{ap17} \cdot y_{67} \cdot (V/div)/y_{17}-$
 $(PS_{ax17}+CL_{17}+PS_{bp17}) \cdot f_{ent} \cdot y_{117}/Vent_{17}+PS_{bx17} \cdot y_{157}/V_{lam17},$
 if $y_{117} < 0$ then $y_{117}=0$ endif,
 $y_{118}'=PS_{ap18} \cdot y_{68} \cdot (V/div)/y_{18}-$
 $(PS_{ax18}+CL_{18}+PS_{bp18}) \cdot f_{ent} \cdot y_{118}/Vent_{18}+PS_{bx18} \cdot y_{158}/V_{lam18},$
 if $y_{118} < 0$ then $y_{118}=0$ endif,
 $y_{119}'=PS_{ap19} \cdot y_{69} \cdot (V/div)/y_{19}-$
 $(PS_{ax19}+CL_{19}+PS_{bp19}) \cdot f_{ent} \cdot y_{119}/Vent_{19}+PS_{bx19} \cdot y_{159}/V_{lam19},$
 if $y_{119} < 0$ then $y_{119}=0$ endif,
 $y_{120}'=PS_{ap20} \cdot y_{70} \cdot (V/div)/y_{20}-$
 $(PS_{ax20}+CL_{20}+PS_{bp20}) \cdot f_{ent} \cdot y_{120}/Vent_{20}+PS_{bx20} \cdot y_{160}/V_{lam20},$
 if $y_{120} < 0$ then $y_{120}=0$ endif,
 $y_{121}'=PS_{ap21} \cdot y_{71} \cdot (V/div)/y_{21}-$
 $(PS_{ax21}+CL_{21}+PS_{bp21}) \cdot f_{ent} \cdot y_{121}/Vent_{21}+PS_{bx21} \cdot y_{161}/V_{lam21},$
 if $y_{121} < 0$ then $y_{121}=0$ endif,
 $y_{122}'=PS_{ap22} \cdot y_{72} \cdot (V/div)/y_{22}-$
 $(PS_{ax22}+CL_{22}+PS_{bp22}) \cdot f_{ent} \cdot y_{122}/Vent_{22}+PS_{bx22} \cdot y_{162}/V_{lam22},$
 if $y_{122} < 0$ then $y_{122}=0$ endif,
 $y_{123}'=PS_{ap23} \cdot y_{73} \cdot (V/div)/y_{23}-$
 $(PS_{ax23}+CL_{23}+PS_{bp23}) \cdot f_{ent} \cdot y_{123}/Vent_{23}+PS_{bx23} \cdot y_{163}/V_{lam23},$
 if $y_{123} < 0$ then $y_{123}=0$ endif,
 $y_{124}'=PS_{ap24} \cdot y_{74} \cdot (V/div)/y_{24}-$
 $(PS_{ax24}+CL_{24}+PS_{bp24}) \cdot f_{ent} \cdot y_{124}/Vent_{24}+PS_{bx24} \cdot y_{164}/V_{lam24},$
 if $y_{124} < 0$ then $y_{124}=0$ endif,

$y_{125}' = PS_{ap25} * y_{75} * (V/div) / y_{25} -$
 $(PS_{ax25} + CL_{25} + PS_{bp25}) * f_{ent} * y_{125} / Vent_{25} + PS_{bx25} * y_{165} / V_{lam25},$
 if $y_{125} < 0$ then $y_{125} = 0$ endif,
 $y_{126}' = PS_{ap26} * y_{76} * (V/div) / y_{26} -$
 $(PS_{ax26} + CL_{26} + PS_{bp26}) * f_{ent} * y_{126} / Vent_{26} + PS_{bx26} * y_{166} / V_{lam26},$
 if $y_{126} < 0$ then $y_{126} = 0$ endif,
 $y_{127}' = PS_{ap27} * y_{77} * (V/div) / y_{27} -$
 $(PS_{ax27} + CL_{27} + PS_{bp27}) * f_{ent} * y_{127} / Vent_{27} + PS_{bx27} * y_{167} / V_{lam27},$
 if $y_{127} < 0$ then $y_{127} = 0$ endif,
 $y_{128}' = PS_{ap28} * y_{78} * (V/div) / y_{28} -$
 $(PS_{ax28} + CL_{28} + PS_{bp28}) * f_{ent} * y_{128} / Vent_{28} + PS_{bx28} * y_{168} / V_{lam28},$
 if $y_{128} < 0$ then $y_{128} = 0$ endif,
 $y_{129}' = PS_{ap29} * y_{79} * (V/div) / y_{29} -$
 $(PS_{ax29} + CL_{29} + PS_{bp29}) * f_{ent} * y_{129} / Vent_{29} + PS_{bx29} * y_{169} / V_{lam29},$
 if $y_{129} < 0$ then $y_{129} = 0$ endif,
 $y_{130}' = PS_{ap30} * y_{80} * (V/div) / y_{30} -$
 $(PS_{ax30} + CL_{30} + PS_{bp30}) * f_{ent} * y_{130} / Vent_{30} + PS_{bx30} * y_{170} / V_{lam30},$
 if $y_{130} < 0$ then $y_{130} = 0$ endif,
 $y_{131}' = PS_{ap31} * y_{81} * (V/div) / y_{31} -$
 $(PS_{ax31} + CL_{31} + PS_{bp31}) * f_{ent} * y_{131} / Vent_{31} + PS_{bx31} * y_{171} / V_{lam31},$
 if $y_{131} < 0$ then $y_{131} = 0$ endif,
 $y_{132}' = PS_{ap32} * y_{82} * (V/div) / y_{32} -$
 $(PS_{ax32} + CL_{32} + PS_{bp32}) * f_{ent} * y_{132} / Vent_{32} + PS_{bx32} * y_{172} / V_{lam32},$
 if $y_{132} < 0$ then $y_{132} = 0$ endif,

$y_{133}' = PS_{ap33} * y_{83} * (V/div) / y_{33}$
 $(PS_{ax33} + CL_{33} + PS_{bp33}) * f_{ent} * y_{133} / Vent_{33} + PS_{bx33} * y_{173} / V_{lam33}$,
 if $y_{133} < 0$ then $y_{133} = 0$ endif,
 $y_{134}' = PS_{ap34} * y_{84} * (V/div) / y_{34}$
 $(PS_{ax34} + CL_{34} + PS_{bp34}) * f_{ent} * y_{134} / Vent_{34} + PS_{bx34} * y_{174} / V_{lam34}$,
 if $y_{134} < 0$ then $y_{134} = 0$ endif,
 $y_{135}' = PS_{ap35} * y_{85} * (V/div) / y_{35}$
 $(PS_{ax35} + CL_{35} + PS_{bp35}) * f_{ent} * y_{135} / Vent_{35} + PS_{bx35} * y_{175} / V_{lam35}$,
 if $y_{135} < 0$ then $y_{135} = 0$ endif,
 $y_{136}' = PS_{ap36} * y_{86} * (V/div) / y_{36}$
 $(PS_{ax36} + CL_{36} + PS_{bp36}) * f_{ent} * y_{136} / Vent_{36} + PS_{bx36} * y_{176} / V_{lam36}$,
 if $y_{136} < 0$ then $y_{136} = 0$ endif,
 $y_{137}' = PS_{ap37} * y_{87} * (V/div) / y_{37}$
 $(PS_{ax37} + CL_{37} + PS_{bp37}) * f_{ent} * y_{137} / Vent_{37} + PS_{bx37} * y_{177} / V_{lam37}$,
 if $y_{137} < 0$ then $y_{137} = 0$ endif,
 $y_{138}' = PS_{ap38} * y_{88} * (V/div) / y_{38}$
 $(PS_{ax38} + CL_{38} + PS_{bp38}) * f_{ent} * y_{138} / Vent_{38} + PS_{bx38} * y_{178} / V_{lam38}$,
 if $y_{138} < 0$ then $y_{138} = 0$ endif,
 $y_{139}' = PS_{ap39} * y_{89} * (V/div) / y_{39}$
 $(PS_{ax39} + CL_{39} + PS_{bp39}) * f_{ent} * y_{139} / Vent_{39} + PS_{bx39} * y_{179} / V_{lam39}$,
 if $y_{139} < 0$ then $y_{139} = 0$ endif,
 $y_{140}' = PS_{ap40} * y_{90} * (V/div) / y_{40}$
 $(PS_{ax40} + CL_{40} + PS_{bp40}) * f_{ent} * y_{140} / Vent_{40} + PS_{bx40} * y_{180} / V_{lam40}$,
 if $y_{140} < 0$ then $y_{140} = 0$ endif,

; Drug amount in the lamina propria

$$y_{141}' = PS_{bp1} * fent * y_{101} / Vent_1 - (Q_{lam1} / fb + PS_{bx1}) * y_{141} / V_{lam1},$$

if $y_{141} < 0$ then $y_{141} = 0$ endif,

$$y_{142}' = PS_{bp2} * fent * y_{102} / Vent_2 - (Q_{lam2} / fb + PS_{bx2}) * y_{142} / V_{lam2},$$

if $y_{142} < 0$ then $y_{142} = 0$ endif,

$$y_{143}' = PS_{bp3} * fent * y_{103} / Vent_3 - (Q_{lam3} / fb + PS_{bx3}) * y_{143} / V_{lam3},$$

if $y_{143} < 0$ then $y_{143} = 0$ endif,

$$y_{144}' = PS_{bp4} * fent * y_{104} / Vent_4 - (Q_{lam4} / fb + PS_{bx4}) * y_{144} / V_{lam4},$$

if $y_{144} < 0$ then $y_{144} = 0$ endif,

$$y_{145}' = PS_{bp5} * fent * y_{105} / Vent_5 - (Q_{lam5} / fb + PS_{bx5}) * y_{145} / V_{lam5},$$

if $y_{145} < 0$ then $y_{145} = 0$ endif,

$$y_{146}' = PS_{bp6} * fent * y_{106} / Vent_6 - (Q_{lam6} / fb + PS_{bx6}) * y_{146} / V_{lam6},$$

if $y_{146} < 0$ then $y_{146} = 0$ endif,

$$y_{147}' = PS_{bp7} * fent * y_{107} / Vent_7 - (Q_{lam7} / fb + PS_{bx7}) * y_{147} / V_{lam7},$$

if $y_{147} < 0$ then $y_{147} = 0$ endif,

$$y_{148}' = PS_{bp8} * fent * y_{108} / Vent_8 - (Q_{lam8} / fb + PS_{bx8}) * y_{148} / V_{lam8},$$

if $y_{148} < 0$ then $y_{148} = 0$ endif,

$$y_{149}' = PS_{bp9} * fent * y_{109} / Vent_9 - (Q_{lam9} / fb + PS_{bx9}) * y_{149} / V_{lam9},$$

if $y_{149} < 0$ then $y_{149} = 0$ endif,

$$y_{150}' = PS_{bp10} * fent * y_{110} / Vent_{10} - (Q_{lam10} / fb + PS_{bx10}) * y_{150} / V_{lam10},$$

if $y_{150} < 0$ then $y_{150} = 0$ endif,

$$y_{151}' = PS_{bp11} * fent * y_{111} / Vent_{11} - (Q_{lam11} / fb + PS_{bx11}) * y_{151} / V_{lam11},$$

if $y_{151} < 0$ then $y_{151} = 0$ endif,

$$y_{152}' = PS_{bp12} * fent * y_{112} / Vent_{12} - (Q_{lam12} / fb + PS_{bx12}) * y_{152} / V_{lam12},$$

if $y_{152} < 0$ then $y_{152} = 0$ endif,

$y_{153}' = PS_{bp13} * f_{ent} * y_{113} / Vent_{13} - (Q_{lam13} / fb + PS_{bx13}) * y_{153} / V_{lam13}$,
 if $y_{153} < 0$ then $y_{153} = 0$ endif,
 $y_{154}' = PS_{bp14} * f_{ent} * y_{114} / Vent_{14} - (Q_{lam14} / fb + PS_{bx14}) * y_{154} / V_{lam14}$,
 if $y_{154} < 0$ then $y_{154} = 0$ endif,
 $y_{155}' = PS_{bp15} * f_{ent} * y_{115} / Vent_{15} - (Q_{lam15} / fb + PS_{bx15}) * y_{155} / V_{lam15}$,
 if $y_{155} < 0$ then $y_{155} = 0$ endif,
 $y_{156}' = PS_{bp16} * f_{ent} * y_{116} / Vent_{16} - (Q_{lam16} / fb + PS_{bx16}) * y_{156} / V_{lam16}$,
 if $y_{156} < 0$ then $y_{156} = 0$ endif,
 $y_{157}' = PS_{bp17} * f_{ent} * y_{117} / Vent_{17} - (Q_{lam17} / fb + PS_{bx17}) * y_{157} / V_{lam17}$,
 if $y_{157} < 0$ then $y_{157} = 0$ endif,
 $y_{158}' = PS_{bp18} * f_{ent} * y_{118} / Vent_{18} - (Q_{lam18} / fb + PS_{bx18}) * y_{158} / V_{lam18}$,
 if $y_{158} < 0$ then $y_{158} = 0$ endif,
 $y_{159}' = PS_{bp19} * f_{ent} * y_{119} / Vent_{19} - (Q_{lam19} / fb + PS_{bx19}) * y_{159} / V_{lam19}$,
 if $y_{159} < 0$ then $y_{159} = 0$ endif,
 $y_{160}' = PS_{bp20} * f_{ent} * y_{120} / Vent_{20} - (Q_{lam20} / fb + PS_{bx20}) * y_{160} / V_{lam20}$,
 if $y_{160} < 0$ then $y_{160} = 0$ endif,
 $y_{161}' = PS_{bp21} * f_{ent} * y_{121} / Vent_{21} - (Q_{lam21} / fb + PS_{bx21}) * y_{161} / V_{lam21}$,
 if $y_{161} < 0$ then $y_{161} = 0$ endif,
 $y_{162}' = PS_{bp22} * f_{ent} * y_{122} / Vent_{22} - (Q_{lam22} / fb + PS_{bx22}) * y_{162} / V_{lam22}$,
 if $y_{162} < 0$ then $y_{162} = 0$ endif,
 $y_{163}' = PS_{bp23} * f_{ent} * y_{123} / Vent_{23} - (Q_{lam23} / fb + PS_{bx23}) * y_{163} / V_{lam23}$,
 if $y_{163} < 0$ then $y_{163} = 0$ endif,
 $y_{164}' = PS_{bp24} * f_{ent} * y_{124} / Vent_{24} - (Q_{lam24} / fb + PS_{bx24}) * y_{164} / V_{lam24}$,
 if $y_{164} < 0$ then $y_{164} = 0$ endif,
 $y_{165}' = PS_{bp25} * f_{ent} * y_{125} / Vent_{25} - (Q_{lam25} / fb + PS_{bx25}) * y_{165} / V_{lam25}$,

if $y_{165} < 0$ then $y_{165}=0$ endif,
 $y_{166}' = PS_{bp26} * f_{ent} * y_{126} / V_{ent26} - (Q_{lam26} / f_b + PS_{bx26}) * y_{166} / V_{lam26}$,
 if $y_{166} < 0$ then $y_{166}=0$ endif,
 $y_{167}' = PS_{bp27} * f_{ent} * y_{127} / V_{ent27} - (Q_{lam27} / f_b + PS_{bx27}) * y_{167} / V_{lam27}$,
 if $y_{167} < 0$ then $y_{167}=0$ endif,
 $y_{168}' = PS_{bp28} * f_{ent} * y_{128} / V_{ent28} - (Q_{lam28} / f_b + PS_{bx28}) * y_{168} / V_{lam28}$,
 if $y_{168} < 0$ then $y_{168}=0$ endif,
 $y_{169}' = PS_{bp29} * f_{ent} * y_{129} / V_{ent29} - (Q_{lam29} / f_b + PS_{bx29}) * y_{169} / V_{lam29}$,
 if $y_{169} < 0$ then $y_{169}=0$ endif,
 $y_{170}' = PS_{bp30} * f_{ent} * y_{130} / V_{ent30} - (Q_{lam30} / f_b + PS_{bx30}) * y_{170} / V_{lam30}$,
 if $y_{170} < 0$ then $y_{170}=0$ endif,
 $y_{171}' = PS_{bp31} * f_{ent} * y_{131} / V_{ent31} - (Q_{lam31} / f_b + PS_{bx31}) * y_{171} / V_{lam31}$,
 if $y_{171} < 0$ then $y_{171}=0$ endif,
 $y_{172}' = PS_{bp32} * f_{ent} * y_{132} / V_{ent32} - (Q_{lam32} / f_b + PS_{bx32}) * y_{172} / V_{lam32}$,
 if $y_{172} < 0$ then $y_{172}=0$ endif,
 $y_{173}' = PS_{bp33} * f_{ent} * y_{133} / V_{ent33} - (Q_{lam33} / f_b + PS_{bx33}) * y_{173} / V_{lam33}$,
 if $y_{173} < 0$ then $y_{173}=0$ endif,
 $y_{174}' = PS_{bp34} * f_{ent} * y_{134} / V_{ent34} - (Q_{lam34} / f_b + PS_{bx34}) * y_{174} / V_{lam34}$,
 if $y_{174} < 0$ then $y_{174}=0$ endif,
 $y_{175}' = PS_{bp35} * f_{ent} * y_{135} / V_{ent35} - (Q_{lam35} / f_b + PS_{bx35}) * y_{175} / V_{lam35}$,
 if $y_{175} < 0$ then $y_{175}=0$ endif,
 $y_{176}' = PS_{bp36} * f_{ent} * y_{136} / V_{ent36} - (Q_{lam36} / f_b + PS_{bx36}) * y_{176} / V_{lam36}$,
 if $y_{176} < 0$ then $y_{176}=0$ endif,
 $y_{177}' = PS_{bp37} * f_{ent} * y_{137} / V_{ent37} - (Q_{lam37} / f_b + PS_{bx37}) * y_{177} / V_{lam37}$,
 if $y_{177} < 0$ then $y_{177}=0$ endif,

$$y178' = PS_{bp38} * f_{ent} * y138 / V_{ent38} - (Q_{lam38} / f_b + PS_{bx38}) * y178 / V_{lam38},$$

if $y178 < 0$ then $y178=0$ endif,

$$y179' = PS_{bp39} * f_{ent} * y139 / V_{ent39} - (Q_{lam39} / f_b + PS_{bx39}) * y179 / V_{lam39},$$

if $y179 < 0$ then $y179=0$ endif,

$$y180' = PS_{bp40} * f_{ent} * y140 / V_{ent40} - (Q_{lam40} / f_b + PS_{bx40}) * y180 / V_{lam40},$$

if $y180 < 0$ then $y180=0$ endif,

; Drug accumulated amount in the portal vein

$$y181' =$$

$$\begin{aligned} & (y141/V_{lam1} * Q_{lam1} + y142/V_{lam2} * Q_{lam2} + y143/V_{lam3} * Q_{lam3} + y144/V_{lam4} * Q_{lam4} + y145 \\ & /V_{lam5} * Q_{lam5} + y146/V_{lam6} * Q_{lam6} + y147/V_{lam7} * Q_{lam7} + y148/V_{lam8} * Q_{lam8} + y149/V_{la} \\ & m9 * Q_{lam9} + y150/V_{lam10} * Q_{lam10} + y151/V_{lam11} * Q_{lam11} + y152/V_{lam12} * Q_{lam12} + y153/V_{la} \\ & lam13 * Q_{lam13} + y154/V_{lam14} * Q_{lam14} + y155/V_{lam15} * Q_{lam15} + y156/V_{lam16} * Q_{lam16} + y1 \\ & 57/V_{lam17} * Q_{lam17} + y158/V_{lam18} * Q_{lam18} + y159/V_{lam19} * Q_{lam19} + y160/V_{lam20} * Q_{lam20} \\ & + y161/V_{lam21} * Q_{lam21} + y162/V_{lam22} * Q_{lam22} + y163/V_{lam23} * Q_{lam23} + y164/V_{lam24} * Q_{la} \\ & m24 + y165/V_{lam25} * Q_{lam25} + y166/V_{lam26} * Q_{lam26} + y167/V_{lam27} * Q_{lam27} + y168/V_{lam28} \\ & * Q_{lam28} + y169/V_{lam29} * Q_{lam29} + y170/V_{lam30} * Q_{lam30} + y171/V_{lam31} * Q_{lam31} + y172/V_{la} \\ & m32 * Q_{lam32} + y173/V_{lam33} * Q_{lam33} + y174/V_{lam34} * Q_{lam34} + y175/V_{lam35} * Q_{lam35} + y176 \\ & /V_{lam36} * Q_{lam36} + y177/V_{lam37} * Q_{lam37} + y178/V_{lam38} * Q_{lam38} + y179/V_{lam39} * Q_{lam39} + \\ & y180/V_{lam40} * Q_{lam40}) / f_b, \end{aligned}$$

; F_A of a substrate

$$y182 = 1 - y91 / \text{dose},$$

; $F_A F_G$ of a substrate

$y_{183} = y_{181}/\text{dose},$

; F_G of a substrate

$y_{184} = y_{183}/y_{182},$

; Intestinal clearance amount (not used in this study)

$y_{185}' = CL_1 * y_{101}/\text{Vent}_1 + CL_2 * y_{102}/\text{Vent}_2 + CL_3 * y_{103}/\text{Vent}_3 + CL_4 * y_{104}/\text{Vent}_4 + CL_5 * y_{105}/\text{Vent}_5 + CL_6 * y_{106}/\text{Vent}_6 + CL_7 * y_{107}/\text{Vent}_7 + CL_8 * y_{108}/\text{Vent}_8 + CL_9 * y_{109}/\text{Vent}_9 + CL_{10} * y_{110}/\text{Vent}_{10} + CL_{11} * y_{111}/\text{Vent}_{11} + CL_{12} * y_{112}/\text{Vent}_{12} + CL_{13} * y_{113}/\text{Vent}_{13} + CL_{14} * y_{114}/\text{Vent}_{14} + CL_{15} * y_{115}/\text{Vent}_{15} + CL_{16} * y_{116}/\text{Vent}_{16} + CL_{17} * y_{117}/\text{Vent}_{17} + CL_{18} * y_{118}/\text{Vent}_{18} + CL_{19} * y_{119}/\text{Vent}_{19} + CL_{20} * y_{120}/\text{Vent}_{20} + CL_{21} * y_{121}/\text{Vent}_{21} + CL_{22} * y_{122}/\text{Vent}_{22} + CL_{23} * y_{123}/\text{Vent}_{23} + CL_{24} * y_{124}/\text{Vent}_{24} + CL_{25} * y_{125}/\text{Vent}_{25} + CL_{26} * y_{126}/\text{Vent}_{26} + CL_{27} * y_{127}/\text{Vent}_{27} + CL_{28} * y_{128}/\text{Vent}_{28} + CL_{29} * y_{129}/\text{Vent}_{29} + CL_{30} * y_{130}/\text{Vent}_{30} + CL_{31} * y_{131}/\text{Vent}_{31} + CL_{32} * y_{132}/\text{Vent}_{32} + CL_{33} * y_{133}/\text{Vent}_{33} + CL_{34} * y_{134}/\text{Vent}_{34} + CL_{35} * y_{135}/\text{Vent}_{35} + CL_{36} * y_{136}/\text{Vent}_{36} + CL_{37} * y_{137}/\text{Vent}_{37} + CL_{38} * y_{138}/\text{Vent}_{38} + CL_{39} * y_{139}/\text{Vent}_{39} + CL_{40} * y_{140}/\text{Vent}_{40},$

; Drug amount in the portal vein

$y_{186}' =$

$(y_{141}/V_{lam1} * Q_{lam1} + y_{142}/V_{lam2} * Q_{lam2} + y_{143}/V_{lam3} * Q_{lam3} + y_{144}/V_{lam4} * Q_{lam4} + y_{145}/V_{lam5} * Q_{lam5} + y_{146}/V_{lam6} * Q_{lam6} + y_{147}/V_{lam7} * Q_{lam7} + y_{148}/V_{lam8} * Q_{lam8} + y_{149}/V_{lam9} * Q_{lam9} + y_{150}/V_{lam10} * Q_{lam10} + y_{151}/V_{lam11} * Q_{lam11} + y_{152}/V_{lam12} * Q_{lam12} + y_{153}/V_{lam13} * Q_{lam13} + y_{154}/V_{lam14} * Q_{lam14} + y_{155}/V_{lam15} * Q_{lam15} + y_{156}/V_{lam16} * Q_{lam16} + y_{157}/V_{lam17} * Q_{lam17} + y_{158}/V_{lam18} * Q_{lam18} + y_{159}/V_{lam19} * Q_{lam19} + y_{160}/V_{lam20} * Q_{lam20} + y_{161}/V_{lam21} * Q_{lam21} + y_{162}/V_{lam22} * Q_{lam22} + y_{163}/V_{lam23} * Q_{lam23} + y_{164}/V_{lam24} * Q_{lam24} + y_{165}/V_{lam25} * Q_{lam25} + y_{166}/V_{lam26} * Q_{lam26} + y_{167}/V_{lam27} * Q_{lam27} + y_{168}/V_{lam28} * Q_{lam28} + y_{169}/V_{lam29} * Q_{lam29} + y_{170}/V_{lam30} * Q_{lam30} + y_{171}/V_{lam31} * Q_{lam31} + y_{172}/V_{lam32} * Q_{lam32} + y_{173}/V_{lam33} * Q_{lam33} + y_{174}/V_{lam34} * Q_{lam34} + y_{175}/V_{lam35} * Q_{lam35} + y_{176}/V_{lam36} * Q_{lam36} + y_{177}/V_{lam37} * Q_{lam37} + y_{178}/V_{lam38} * Q_{lam38} + y_{179}/V_{lam39} * Q_{lam39} + y_{180}/V_{lam40} * Q_{lam40})$

*Qlam28+y169/Vlam29*Qlam29+y170/Vlam30*Qlam30+y171/Vlam31*Qlam31+y172/Vlam32*Qlam32+y173/Vlam33*Qlam33+y174/Vlam34*Qlam34+y175/Vlam35*Qlam35+y176/Vlam36*Qlam36+y177/Vlam37*Qlam37+y178/Vlam38*Qlam38+y179/Vlam39*Qlam39+y180/Vlam40*Qlam40)/fb-Qpv*y186/Vpv,

; Drug concentration in the liver

y187'=(Qpv*y186/Vpv-Qh*y187/Kp_liver*Rb-fb*Rb/Kp_liver*CLint_h/(1+fb_inh*y330/Ki_3A4)*y187+Qha*y188)/Vliver,

; Drug concentration in the blood

y188'=(Qh*y187/Kp_liver*Rb-Qha*y188-k12*y188*Vb+k21*y189)/Vb,

; Drug amount in the peripheral compartment 1

; The number of compartments can be increased as necessary

y189'=k12*y188*Vb-k21*y189,

; Drug concentration in the plasma (unit: umol/L)

y190=y188/MW/Rb*1000,

; Following is the codes about an inhibitor

; Membrane permeability of an inhibitor

Ppass_lum_a1_inh = P_invivo_inh (1+10^(pH_Caco2-pKa_acid_inh)+10^(pKa_base_inh-pH_Caco2))/(1+10^(pH_lum1-pKa_acid_inh)+10^(pKa_base_inh-pH_lum1)),

PSpass_lum_a1_inh= Ppass_lum_a1_inh ME Sent1,

$$P_{\text{Spa}}_{a1_inh} = P_{\text{invivo_inh}} \text{ ME Sent1},$$

$$P_{\text{Spa}}_{b1_inh} = P_{\text{invivo_inh}} \text{ Sent1},$$

$$P_{\text{Sap}}_{1_inh} = P_{\text{Spa}}_{lum_a1_inh},$$

$$P_{\text{Sbp}}_{1_inh} = P_{\text{Spa}}_{b1_inh},$$

$$P_{\text{Sbx}}_{1_inh} = P_{\text{Spa}}_{b1_inh},$$

$$P_{\text{Spgp}}_{1_inh} = \text{psf_Pgp} * V_{\text{max_Pgp_inh}} * A_{\text{rel_Pgp1}} / (K_{\text{m_Pgp_inh}} + f_{\text{ent_inh}} * y_{231} / V_{\text{ent1}}),$$

$$P_{\text{Sax}}_{1_inh} = (P_{\text{Spa}}_{a1_inh} + P_{\text{Spgp}}_{1_inh}),$$

$$CL_{1_inh} = V_{\text{max_3A4_inh}} * A_{\text{rel_3A4_1}} / (K_{\text{m_3A4_inh}} + f_{\text{ent_inh}} * y_{231} / V_{\text{ent1}}),$$

$$P_{\text{pass_lum_a2_inh}} = P_{\text{invivo_inh}} (1 + 10^{(\text{pH_Caco2} - \text{pKa_acid_inh})} + 10^{(\text{pKa_base_inh} - \text{pH_Caco2})}) / (1 + 10^{(\text{pH_lum2} - \text{pKa_acid_inh})} + 10^{(\text{pKa_base_inh} - \text{pH_lum2})}),$$

$$P_{\text{Spa}}_{lum_a2_inh} = P_{\text{pass_lum_a2_inh}} \text{ ME Sent2},$$

$$P_{\text{Spa}}_{a2_inh} = P_{\text{invivo_inh}} \text{ ME Sent2},$$

$$P_{\text{Spa}}_{b2_inh} = P_{\text{invivo_inh}} \text{ Sent2},$$

$$P_{\text{Sap}}_{2_inh} = P_{\text{Spa}}_{lum_a2_inh},$$

$$P_{\text{Sbp}}_{2_inh} = P_{\text{Spa}}_{b2_inh},$$

$$P_{\text{Sbx}}_{2_inh} = P_{\text{Spa}}_{b2_inh},$$

$$P_{\text{Spgp}}_{2_inh} = \text{psf_Pgp} * V_{\text{max_Pgp_inh}} * A_{\text{rel_Pgp2}} / (K_{\text{m_Pgp_inh}} + f_{\text{ent_inh}} * y_{232} / V_{\text{ent2}}),$$

$$P_{\text{Sax}}_{2_inh} = (P_{\text{Spa}}_{a2_inh} + P_{\text{Spgp}}_{2_inh}),$$

$$CL_{2_inh} = V_{\text{max_3A4_inh}} * A_{\text{rel_3A4_2}} / (K_{\text{m_3A4_inh}} + f_{\text{ent_inh}} * y_{232} / V_{\text{ent2}}),$$

$$P_{\text{pass_lum_a3_inh}} = P_{\text{invivo_inh}} (1 + 10^{(\text{pH_Caco2} - \text{pKa_acid_inh})} + 10^{(\text{pKa_base_inh} - \text{pH_Caco2})}) / (1 + 10^{(\text{pH_lum3} - \text{pKa_acid_inh})} + 10^{(\text{pKa_base_inh} - \text{pH_lum3})}),$$

$$P_{\text{Spass_lum_a3_inh}} = P_{\text{pass_lum_a3_inh}} \text{ ME Sent3,}$$

$$P_{\text{Spass_a3_inh}} = P_{\text{invivo_inh}} \text{ ME Sent3,}$$

$$P_{\text{Spass_b3_inh}} = P_{\text{invivo_inh}} \text{ Sent3,}$$

$$P_{\text{Sap3_inh}} = P_{\text{Spass_lum_a3_inh}},$$

$$P_{\text{Sbp3_inh}} = P_{\text{Spass_b3_inh}},$$

$$P_{\text{Sbx3_inh}} = P_{\text{Spass_b3_inh}},$$

$$P_{\text{Spgp3_inh}} = \text{psf_Pgp} * V_{\text{max_Pgp_inh}} * A_{\text{rel_Pgp3}} / (K_{\text{m_Pgp_inh}} + f_{\text{ent_inh}} * y_{233} / V_{\text{ent3}}),$$

$$P_{\text{Sax3_inh}} = (P_{\text{Spass_a3_inh}} + P_{\text{Spgp3_inh}}),$$

$$CL_{3_inh} = V_{\text{max_3A4_inh}} * A_{\text{rel_3A4_3}} / (K_{\text{m_3A4_inh}} + f_{\text{ent_inh}} * y_{233} / V_{\text{ent3}}),$$

$$P_{\text{pass_lum_a4_inh}} = P_{\text{invivo_inh}} (1 + 10^{(\text{pH_Caco2} - \text{pKa_acid_inh})} + 10^{(\text{pKa_base_inh} - \text{pH_Caco2})}) / (1 + 10^{(\text{pH_lum4} - \text{pKa_acid_inh})}$$

$$+ 10^{(\text{pKa_base_inh} - \text{pH_lum4})}),$$

$$P_{\text{Spass_lum_a4_inh}} = P_{\text{pass_lum_a4_inh}} \text{ ME Sent4,}$$

$$P_{\text{Spass_a4_inh}} = P_{\text{invivo_inh}} \text{ ME Sent4,}$$

$$P_{\text{Spass_b4_inh}} = P_{\text{invivo_inh}} \text{ Sent4,}$$

$$P_{\text{Sap4_inh}} = P_{\text{Spass_lum_a4_inh}},$$

$$P_{\text{Sbp4_inh}} = P_{\text{Spass_b4_inh}},$$

$$P_{\text{Sbx4_inh}} = P_{\text{Spass_b4_inh}},$$

$$P_{\text{Spgp4_inh}} = \text{psf_Pgp} * V_{\text{max_Pgp_inh}} * A_{\text{rel_Pgp4}} / (K_{\text{m_Pgp_inh}} + f_{\text{ent_inh}} * y_{234} / V_{\text{ent4}}),$$

$$P_{\text{Sax4_inh}} = (P_{\text{Spass_a4_inh}} + P_{\text{Spgp4_inh}}),$$

$$CL_{4_inh} = V_{\text{max_3A4_inh}} * A_{\text{rel_3A4_4}} / (K_{\text{m_3A4_inh}} + f_{\text{ent_inh}} * y_{234} / V_{\text{ent4}}),$$

$$P_{\text{pass_lum_a5_inh}} = P_{\text{invivo_inh}} (1 + 10^{(\text{pH_Caco2} - \text{pKa_acid_inh})} + 10^{(\text{pKa_base_inh} - \text{pH_Caco2})}) / (1 + 10^{(\text{pH_lum5} - \text{pKa_acid_inh})}$$

$+10^{(pKa_base_inh-pH_lum5)}$),
 $PSpass_lum_a5_inh = Ppass_lum_a5_inh ME Sent5$,
 $PSpass_a5_inh = P_invivo_inh ME Sent5$,
 $PSpass_b5_inh = P_invivo_inh Sent5$,
 $PSap5_inh = PSpass_lum_a5_inh$,
 $PSbp5_inh = PSpass_b5_inh$,
 $PSbx5_inh = PSpass_b5_inh$,
 $PSpgp5_inh = psf_Pgp * Vmax_Pgp_inh * Arel_Pgp5 / (Km_Pgp_inh + fent_inh * y235 / Vent5)$,
 $PSax5_inh = (PSpass_a5_inh + PSpgp5_inh)$,
 $CL5_inh = Vmax_3A4_inh * Arel_3A4_5 / (Km_3A4_inh + fent_inh * y235 / Vent5)$,

$Ppass_lum_a6_inh = P_invivo_inh (1 + 10^{(pH_Caco2-pKa_acid_inh)} + 10^{(pKa_base_inh - pH_Caco2)}) / (1 + 10^{(pH_lum6-pKa_acid_inh)} + 10^{(pKa_base_inh - pH_lum6)})$),
 $PSpass_lum_a6_inh = Ppass_lum_a6_inh ME Sent6$,
 $PSpass_a6_inh = P_invivo_inh ME Sent6$,
 $PSpass_b6_inh = P_invivo_inh Sent6$,
 $PSap6_inh = PSpass_lum_a6_inh$,
 $PSbp6_inh = PSpass_b6_inh$,
 $PSbx6_inh = PSpass_b6_inh$,
 $PSpgp6_inh = psf_Pgp * Vmax_Pgp_inh * Arel_Pgp6 / (Km_Pgp_inh + fent_inh * y236 / Vent6)$,
 $PSax6_inh = (PSpass_a6_inh + PSpgp6_inh)$,
 $CL6_inh = Vmax_3A4_inh * Arel_3A4_6 / (Km_3A4_inh + fent_inh * y236 / Vent6)$,

$$P_{\text{pass_lum_a7_inh}} = P_{\text{invivo_inh}} \left(\frac{1 + 10^{(\text{pH_Caco2} - \text{pKa_acid_inh})} + 10^{(\text{pKa_base_inh} - \text{pH_Caco2})}}{1 + 10^{(\text{pH_lum7} - \text{pKa_acid_inh})}} \right)$$

$$+ 10^{(\text{pKa_base_inh} - \text{pH_lum7})},$$

$$P_{\text{Spass_lum_a7_inh}} = P_{\text{pass_lum_a7_inh}} \text{ ME Sent7},$$

$$P_{\text{Spass_a7_inh}} = P_{\text{invivo_inh}} \text{ ME Sent7},$$

$$P_{\text{Spass_b7_inh}} = P_{\text{invivo_inh}} \text{ Sent7},$$

$$P_{\text{Sap7_inh}} = P_{\text{Spass_lum_a7_inh}},$$

$$P_{\text{Sbp7_inh}} = P_{\text{Spass_b7_inh}},$$

$$P_{\text{Sbx7_inh}} = P_{\text{Spass_b7_inh}},$$

$$P_{\text{Spgp7_inh}} = \text{psf_Pgp} * V_{\text{max_Pgp_inh}} * A_{\text{rel_Pgp7}} / (K_{\text{m_Pgp_inh}} + \text{fent_inh} * y_{237} / V_{\text{ent7}}),$$

$$P_{\text{Sax7_inh}} = (P_{\text{Spass_a7_inh}} + P_{\text{Spgp7_inh}}),$$

$$CL_{7_inh} = V_{\text{max_3A4_inh}} * A_{\text{rel_3A4_7}} / (K_{\text{m_3A4_inh}} + \text{fent_inh} * y_{237} / V_{\text{ent7}}),$$

$$P_{\text{pass_lum_a8_inh}} = P_{\text{invivo_inh}} \left(\frac{1 + 10^{(\text{pH_Caco2} - \text{pKa_acid_inh})} + 10^{(\text{pKa_base_inh} - \text{pH_Caco2})}}{1 + 10^{(\text{pH_lum8} - \text{pKa_acid_inh})}} \right)$$

$$+ 10^{(\text{pKa_base_inh} - \text{pH_lum8})},$$

$$P_{\text{Spass_lum_a8_inh}} = P_{\text{pass_lum_a8_inh}} \text{ ME Sent8},$$

$$P_{\text{Spass_a8_inh}} = P_{\text{invivo_inh}} \text{ ME Sent8},$$

$$P_{\text{Spass_b8_inh}} = P_{\text{invivo_inh}} \text{ Sent8},$$

$$P_{\text{Sap8_inh}} = P_{\text{Spass_lum_a8_inh}},$$

$$P_{\text{Sbp8_inh}} = P_{\text{Spass_b8_inh}},$$

$$P_{\text{Sbx8_inh}} = P_{\text{Spass_b8_inh}},$$

$$P_{\text{Spgp8_inh}} = \text{psf_Pgp} * V_{\text{max_Pgp_inh}} * A_{\text{rel_Pgp8}} / (K_{\text{m_Pgp_inh}} + \text{fent_inh} * y_{238} / V_{\text{ent8}}),$$

$$P_{\text{Sax8_inh}} = (P_{\text{Spass_a8_inh}} + P_{\text{Spgp8_inh}}),$$

$$CL_{8_inh} = V_{\text{max_3A4_inh}} * A_{\text{rel_3A4_8}} / (K_{\text{m_3A4_inh}} + \text{fent_inh} * y_{238} / V_{\text{ent8}}),$$

$$P_{\text{pass_lum_a9_inh}} = P_{\text{invivo_inh}} \left(\frac{1 + 10^{(\text{pH_Caco2} - \text{pKa_acid_inh})} + 10^{(\text{pKa_base_inh} - \text{pH_Caco2})}}{1 + 10^{(\text{pH_lum9} - \text{pKa_acid_inh})} + 10^{(\text{pKa_base_inh} - \text{pH_lum9})}} \right)$$

$$+ 10^{(\text{pKa_base_inh} - \text{pH_lum9})},$$

$$P_{\text{Spass_lum_a9_inh}} = P_{\text{pass_lum_a9_inh}} \text{ ME Sent9},$$

$$P_{\text{Spass_a9_inh}} = P_{\text{invivo_inh}} \text{ ME Sent9},$$

$$P_{\text{Spass_b9_inh}} = P_{\text{invivo_inh}} \text{ Sent9},$$

$$P_{\text{Sap9_inh}} = P_{\text{Spass_lum_a9_inh}},$$

$$P_{\text{Sbp9_inh}} = P_{\text{Spass_b9_inh}},$$

$$P_{\text{Sbx9_inh}} = P_{\text{Spass_b9_inh}},$$

$$P_{\text{Spgp9_inh}} = \text{psf_Pgp} * V_{\text{max_Pgp_inh}} * A_{\text{rel_Pgp9}} / (K_{\text{m_Pgp_inh}} + \text{fent_inh} * y_{239} / V_{\text{ent9}}),$$

$$P_{\text{Sax9_inh}} = (P_{\text{Spass_a9_inh}} + P_{\text{Spgp9_inh}}),$$

$$CL_{9_inh} = V_{\text{max_3A4_inh}} * A_{\text{rel_3A4_9}} / (K_{\text{m_3A4_inh}} + \text{fent_inh} * y_{239} / V_{\text{ent9}}),$$

$$P_{\text{pass_lum_a10_inh}} = P_{\text{invivo_inh}} \left(\frac{1 + 10^{(\text{pH_Caco2} - \text{pKa_acid_inh})} + 10^{(\text{pKa_base_inh} - \text{pH_Caco2})}}{1 + 10^{(\text{pH_lum10} - \text{pKa_acid_inh})} + 10^{(\text{pKa_base_inh} - \text{pH_lum10})}} \right)$$

$$+ 10^{(\text{pKa_base_inh} - \text{pH_lum10})},$$

$$P_{\text{Spass_lum_a10_inh}} = P_{\text{pass_lum_a10_inh}} \text{ ME Sent10},$$

$$P_{\text{Spass_a10_inh}} = P_{\text{invivo_inh}} \text{ ME Sent10},$$

$$P_{\text{Spass_b10_inh}} = P_{\text{invivo_inh}} \text{ Sent10},$$

$$P_{\text{Sap10_inh}} = P_{\text{Spass_lum_a10_inh}},$$

$$P_{\text{Sbp10_inh}} = P_{\text{Spass_b10_inh}},$$

$$P_{\text{Sbx10_inh}} = P_{\text{Spass_b10_inh}},$$

$$P_{\text{Spgp10_inh}} = \text{psf_Pgp} * V_{\text{max_Pgp_inh}} * A_{\text{rel_Pgp10}}$$

$$/ (K_{\text{m_Pgp_inh}} + \text{fent_inh} * y_{240} / V_{\text{ent10}}),$$

$$PSax10_inh = (PSpass_a10_inh + PSpgp10_inh),$$

$$CL10_inh = Vmax_3A4_inh * Arel_3A4_10 / (Km_3A4_inh + fent_inh * y240 / Vent10),$$

$$Ppass_lum_a11_inh = P_invivo_inh (1 + 10^{(pH_Caco2 - pKa_acid_inh)} + 10^{(pKa_base_inh - pH_Caco2)}) / (1 + 10^{(pH_lum11 - pKa_acid_inh)}$$

$$+ 10^{(pKa_base_inh - pH_lum11)}),$$

$$PSpass_lum_a11_inh = Ppass_lum_a11_inh ME Sent11,$$

$$PSpass_a11_inh = P_invivo_inh ME Sent11,$$

$$PSpass_b11_inh = P_invivo_inh Sent11,$$

$$PSap11_inh = PSpass_lum_a11_inh,$$

$$PSbp11_inh = PSpass_b11_inh,$$

$$PSbx11_inh = PSpass_b11_inh,$$

$$PSpgp11_inh = psf_Pgp * Vmax_Pgp_inh * Arel_Pgp11$$

$$/ (Km_Pgp_inh + fent_inh * y241 / Vent11),$$

$$PSax11_inh = (PSpass_a11_inh + PSpgp11_inh),$$

$$CL11_inh = Vmax_3A4_inh * Arel_3A4_11 / (Km_3A4_inh + fent_inh * y241 / Vent11),$$

$$Ppass_lum_a12_inh = P_invivo_inh (1 + 10^{(pH_Caco2 - pKa_acid_inh)} + 10^{(pKa_base_inh - pH_Caco2)}) / (1 + 10^{(pH_lum12 - pKa_acid_inh)}$$

$$+ 10^{(pKa_base_inh - pH_lum12)}),$$

$$PSpass_lum_a12_inh = Ppass_lum_a12_inh ME Sent12,$$

$$PSpass_a12_inh = P_invivo_inh ME Sent12,$$

$$PSpass_b12_inh = P_invivo_inh Sent12,$$

$$PSap12_inh = PSpass_lum_a12_inh,$$

$$PSbp12_inh = PSpass_b12_inh,$$

PSbx12_inh = PSpass_b12_inh,

PSpgp12_inh = psf_Pgp*Vmax_Pgp_inh*Arel_Pgp12

/(Km_Pgp_inh+fent_inh*y242/Vent12),

PSax12_inh = (PSpass_a12_inh+ PSpgp12_inh),

CL12_inh = Vmax_3A4_inh*Arel_3A4_12/(Km_3A4_inh+fent_inh*y242/Vent12),

Ppass_lum_a13_inh = P_invivo_inh (1+10^(pH_Caco2-pKa_acid_inh)+10^(pKa_base_inh-
pH_Caco2))/(1+10^(pH_lum13-pKa_acid_inh)

+10^(pKa_base_inh-pH_lum13)),

PSpass_lum_a13_inh= Ppass_lum_a13_inh ME Sent13,

PSpass_a13_inh = P_invivo_inh ME Sent13,

PSpass_b13_inh = P_invivo_inh Sent13,

PSap13_inh = PSpass_lum_a13_inh,

PSbp13_inh = PSpass_b13_inh,

PSbx13_inh = PSpass_b13_inh,

PSpgp13_inh = psf_Pgp*Vmax_Pgp_inh*Arel_Pgp13

/(Km_Pgp_inh+fent_inh*y243/Vent13),

PSax13_inh = (PSpass_a13_inh+ PSpgp13_inh),

CL13_inh = Vmax_3A4_inh*Arel_3A4_13/(Km_3A4_inh+fent_inh*y243/Vent13),

Ppass_lum_a14_inh = P_invivo_inh (1+10^(pH_Caco2-pKa_acid_inh)+10^(pKa_base_inh-
pH_Caco2))/(1+10^(pH_lum14-pKa_acid_inh)

+10^(pKa_base_inh-pH_lum14)),

PSpass_lum_a14_inh= Ppass_lum_a14_inh ME Sent14,

PSpass_a14_inh = P_invivo_inh ME Sent14,

$$P_{\text{Spass_b14_inh}} = P_{\text{invivo_inh}} \text{ Sent14},$$

$$P_{\text{Sap14_inh}} = P_{\text{Spass_lum_a14_inh}},$$

$$P_{\text{Sbp14_inh}} = P_{\text{Spass_b14_inh}},$$

$$P_{\text{Sbx14_inh}} = P_{\text{Spass_b14_inh}},$$

$$P_{\text{Spgp14_inh}} = \text{psf_Pgp} * V_{\text{max_Pgp_inh}} * A_{\text{rel_Pgp14}}$$

$$/ (K_{\text{m_Pgp_inh}} + f_{\text{ent_inh}} * y_{244} / V_{\text{ent14}}),$$

$$P_{\text{Sax14_inh}} = (P_{\text{Spass_a14_inh}} + P_{\text{Spgp14_inh}}),$$

$$CL_{14_inh} = V_{\text{max_3A4_inh}} * A_{\text{rel_3A4_14}} / (K_{\text{m_3A4_inh}} + f_{\text{ent_inh}} * y_{244} / V_{\text{ent14}}),$$

$$P_{\text{pass_lum_a15_inh}} = P_{\text{invivo_inh}} \frac{(1 + 10^{(\text{pH_Caco2} - \text{pKa_acid_inh})} + 10^{(\text{pKa_base_inh} - \text{pH_Caco2})})}{(1 + 10^{(\text{pH_lum15} - \text{pKa_acid_inh})} + 10^{(\text{pKa_base_inh} - \text{pH_lum15})}),$$

$$P_{\text{Spass_lum_a15_inh}} = P_{\text{pass_lum_a15_inh}} \text{ ME Sent15},$$

$$P_{\text{Spass_a15_inh}} = P_{\text{invivo_inh}} \text{ ME Sent15},$$

$$P_{\text{Spass_b15_inh}} = P_{\text{invivo_inh}} \text{ Sent15},$$

$$P_{\text{Sap15_inh}} = P_{\text{Spass_lum_a15_inh}},$$

$$P_{\text{Sbp15_inh}} = P_{\text{Spass_b15_inh}},$$

$$P_{\text{Sbx15_inh}} = P_{\text{Spass_b15_inh}},$$

$$P_{\text{Spgp15_inh}} = \text{psf_Pgp} * V_{\text{max_Pgp_inh}} * A_{\text{rel_Pgp15}}$$

$$/ (K_{\text{m_Pgp_inh}} + f_{\text{ent_inh}} * y_{245} / V_{\text{ent15}}),$$

$$P_{\text{Sax15_inh}} = (P_{\text{Spass_a15_inh}} + P_{\text{Spgp15_inh}}),$$

$$CL_{15_inh} = V_{\text{max_3A4_inh}} * A_{\text{rel_3A4_15}} / (K_{\text{m_3A4_inh}} + f_{\text{ent_inh}} * y_{245} / V_{\text{ent15}}),$$

$$P_{\text{pass_lum_a16_inh}} = P_{\text{invivo_inh}} \frac{(1 + 10^{(\text{pH_Caco2} - \text{pKa_acid_inh})} + 10^{(\text{pKa_base_inh} - \text{pH_Caco2})})}{(1 + 10^{(\text{pH_lum16} - \text{pKa_acid_inh})}}$$

$+10^{(pKa_base_inh-pH_lum16)},$
 $PSpass_lum_a16_inh = Ppass_lum_a16_inh \text{ ME Sent16},$
 $PSpass_a16_inh = P_invivo_inh \text{ ME Sent16},$
 $PSpass_b16_inh = P_invivo_inh \text{ Sent16},$
 $PSap16_inh = PSpass_lum_a16_inh,$
 $PSbp16_inh = PSpass_b16_inh,$
 $PSbx16_inh = PSpass_b16_inh,$
 $PSpgp16_inh = psf_Pgp * Vmax_Pgp_inh * Arel_Pgp16$
 $/(Km_Pgp_inh + fent_inh * y246 / Vent16),$
 $PSax16_inh = (PSpass_a16_inh + PSpgp16_inh),$
 $CL16_inh = Vmax_3A4_inh * Arel_3A4_16 / (Km_3A4_inh + fent_inh * y246 / Vent16),$

$Ppass_lum_a17_inh = P_invivo_inh (1 + 10^{(pH_Caco2 - pKa_acid_inh)} + 10^{(pKa_base_inh - pH_Caco2)}) / (1 + 10^{(pH_lum17 - pKa_acid_inh)}$
 $+ 10^{(pKa_base_inh - pH_lum17)}),$
 $PSpass_lum_a17_inh = Ppass_lum_a17_inh \text{ ME Sent17},$
 $PSpass_a17_inh = P_invivo_inh \text{ ME Sent17},$
 $PSpass_b17_inh = P_invivo_inh \text{ Sent17},$
 $PSap17_inh = PSpass_lum_a17_inh,$
 $PSbp17_inh = PSpass_b17_inh,$
 $PSbx17_inh = PSpass_b17_inh,$
 $PSpgp17_inh = psf_Pgp * Vmax_Pgp_inh * Arel_Pgp17$
 $/(Km_Pgp_inh + fent_inh * y247 / Vent17),$
 $PSax17_inh = (PSpass_a17_inh + PSpgp17_inh),$
 $CL17_inh = Vmax_3A4_inh * Arel_3A4_17 / (Km_3A4_inh + fent_inh * y247 / Vent17),$

$$P_{\text{pass_lum_a18_inh}} = P_{\text{invivo_inh}} \left(\frac{1 + 10^{(\text{pH_Caco2} - \text{pKa_acid_inh})} + 10^{(\text{pKa_base_inh} - \text{pH_Caco2})}}{1 + 10^{(\text{pH_lum18} - \text{pKa_acid_inh})} + 10^{(\text{pKa_base_inh} - \text{pH_lum18})}} \right)$$

$$P_{\text{Spass_lum_a18_inh}} = P_{\text{pass_lum_a18_inh}} \text{ ME Sent18,}$$

$$P_{\text{Spass_a18_inh}} = P_{\text{invivo_inh}} \text{ ME Sent18,}$$

$$P_{\text{Spass_b18_inh}} = P_{\text{invivo_inh}} \text{ Sent18,}$$

$$P_{\text{Sap18_inh}} = P_{\text{Spass_lum_a18_inh}},$$

$$P_{\text{Sbp18_inh}} = P_{\text{Spass_b18_inh}},$$

$$P_{\text{Sbx18_inh}} = P_{\text{Spass_b18_inh}},$$

$$P_{\text{Spgp18_inh}} = \frac{\text{psf_Pgp} * V_{\text{max_Pgp_inh}} * A_{\text{rel_Pgp18}}}{(K_{\text{m_Pgp_inh}} + \text{fent_inh} * y_{248} / V_{\text{ent18}})},$$

$$P_{\text{Sax18_inh}} = (P_{\text{Spass_a18_inh}} + P_{\text{Spgp18_inh}}),$$

$$CL_{18_inh} = \frac{V_{\text{max_3A4_inh}} * A_{\text{rel_3A4_18}}}{(K_{\text{m_3A4_inh}} + \text{fent_inh} * y_{248} / V_{\text{ent18}})},$$

$$P_{\text{pass_lum_a19_inh}} = P_{\text{invivo_inh}} \left(\frac{1 + 10^{(\text{pH_Caco2} - \text{pKa_acid_inh})} + 10^{(\text{pKa_base_inh} - \text{pH_Caco2})}}{1 + 10^{(\text{pH_lum19} - \text{pKa_acid_inh})} + 10^{(\text{pKa_base_inh} - \text{pH_lum19})}} \right)$$

$$P_{\text{Spass_lum_a19_inh}} = P_{\text{pass_lum_a19_inh}} \text{ ME Sent19,}$$

$$P_{\text{Spass_a19_inh}} = P_{\text{invivo_inh}} \text{ ME Sent19,}$$

$$P_{\text{Spass_b19_inh}} = P_{\text{invivo_inh}} \text{ Sent19,}$$

$$P_{\text{Sap19_inh}} = P_{\text{Spass_lum_a19_inh}},$$

$$P_{\text{Sbp19_inh}} = P_{\text{Spass_b19_inh}},$$

$$P_{\text{Sbx19_inh}} = P_{\text{Spass_b19_inh}},$$

$$PSpgp19_inh = psf_Pgp * Vmax_Pgp_inh * Arel_Pgp19$$

$$/(Km_Pgp_inh + fent_inh * y249 / Vent19),$$

$$PSax19_inh = (PSpass_a19_inh + PSpgp19_inh),$$

$$CL19_inh = Vmax_3A4_inh * Arel_3A4_19 / (Km_3A4_inh + fent_inh * y249 / Vent19),$$

$$Ppass_lum_a20_inh = P_invivo_inh (1 + 10^{(pH_Caco2 - pKa_acid_inh)} + 10^{(pKa_base_inh -$$

$$pH_Caco2)) / (1 + 10^{(pH_lum20 - pKa_acid_inh)}$$

$$+ 10^{(pKa_base_inh - pH_lum20)}),$$

$$PSpass_lum_a20_inh = Ppass_lum_a20_inh ME Sent20,$$

$$PSpass_a20_inh = P_invivo_inh ME Sent20,$$

$$PSpass_b20_inh = P_invivo_inh Sent20,$$

$$PSap20_inh = PSpass_lum_a20_inh,$$

$$PSbp20_inh = PSpass_b20_inh,$$

$$PSbx20_inh = PSpass_b20_inh,$$

$$PSpgp20_inh = psf_Pgp * Vmax_Pgp_inh * Arel_Pgp20$$

$$/(Km_Pgp_inh + fent_inh * y250 / Vent20),$$

$$PSax20_inh = (PSpass_a20_inh + PSpgp20_inh),$$

$$CL20_inh = Vmax_3A4_inh * Arel_3A4_20 / (Km_3A4_inh + fent_inh * y250 / Vent20),$$

$$Ppass_lum_a21_inh = P_invivo_inh (1 + 10^{(pH_Caco2 - pKa_acid_inh)} + 10^{(pKa_base_inh -$$

$$pH_Caco2)) / (1 + 10^{(pH_lum21 - pKa_acid_inh)}$$

$$+ 10^{(pKa_base_inh - pH_lum21)}),$$

$$PSpass_lum_a21_inh = Ppass_lum_a21_inh ME Sent21,$$

$$PSpass_a21_inh = P_invivo_inh ME Sent21,$$

$$PSpass_b21_inh = P_invivo_inh Sent21,$$

$$PSap21_inh = PSpass_lum_a21_inh,$$

$$PSbp21_inh = PSpass_b21_inh,$$

$$PSbx21_inh = PSpass_b21_inh,$$

$$PSpgp21_inh = psf_Pgp * Vmax_Pgp_inh * Arel_Pgp21$$

$$/(Km_Pgp_inh + fent_inh * y251 / Vent21),$$

$$PSax21_inh = (PSpass_a21_inh + PSpgp21_inh),$$

$$CL21_inh = Vmax_3A4_inh * Arel_3A4_21 / (Km_3A4_inh + fent_inh * y251 / Vent21),$$

$$Ppass_lum_a22_inh = P_invivo_inh (1 + 10^{(pH_Caco2 - pKa_acid_inh)} + 10^{(pKa_base_inh - pH_Caco2)}) / (1 + 10^{(pH_lum22 - pKa_acid_inh)}$$

$$+ 10^{(pKa_base_inh - pH_lum22)}),$$

$$PSpass_lum_a22_inh = Ppass_lum_a22_inh ME Sent22,$$

$$PSpass_a22_inh = P_invivo_inh ME Sent22,$$

$$PSpass_b22_inh = P_invivo_inh Sent22,$$

$$PSap22_inh = PSpass_lum_a22_inh,$$

$$PSbp22_inh = PSpass_b22_inh,$$

$$PSbx22_inh = PSpass_b22_inh,$$

$$PSpgp22_inh = psf_Pgp * Vmax_Pgp_inh * Arel_Pgp22$$

$$/(Km_Pgp_inh + fent_inh * y252 / Vent22),$$

$$PSax22_inh = (PSpass_a22_inh + PSpgp22_inh),$$

$$CL22_inh = Vmax_3A4_inh * Arel_3A4_22 / (Km_3A4_inh + fent_inh * y252 / Vent22),$$

$$Ppass_lum_a23_inh = P_invivo_inh (1 + 10^{(pH_Caco2 - pKa_acid_inh)} + 10^{(pKa_base_inh - pH_Caco2)}) / (1 + 10^{(pH_lum23 - pKa_acid_inh)}$$

$$+ 10^{(pKa_base_inh - pH_lum23)}),$$

PSpass_lum_a23_inh= Ppass_lum_a23_inh ME Sent23,

PSpass_a23_inh = P_invivo_inh ME Sent23,

PSpass_b23_inh = P_invivo_inh Sent23,

PSap23_inh = PSpass_lum_a23_inh,

PSbp23_inh = PSpass_b23_inh,

PSbx23_inh = PSpass_b23_inh,

PSpgp23_inh = psf_Pgp*Vmax_Pgp_inh*Arel_Pgp23

/(Km_Pgp_inh+fent_inh*y253/Vent23),

PSax23_inh = (PSpass_a23_inh+ PSpgp23_inh),

CL23_inh = Vmax_3A4_inh*Arel_3A4_23 /(Km_3A4_inh+fent_inh*y253/Vent23),

Ppass_lum_a24_inh = P_invivo_inh (1+10^(pH_Caco2-pKa_acid_inh)+10^(pKa_base_inh-
pH_Caco2))/(1+10^(pH_lum24-pKa_acid_inh)
+10^(pKa_base_inh-pH_lum24)),

PSpass_lum_a24_inh= Ppass_lum_a24_inh ME Sent24,

PSpass_a24_inh = P_invivo_inh ME Sent24,

PSpass_b24_inh = P_invivo_inh Sent24,

PSap24_inh = PSpass_lum_a24_inh,

PSbp24_inh = PSpass_b24_inh,

PSbx24_inh = PSpass_b24_inh,

PSpgp24_inh = psf_Pgp*Vmax_Pgp_inh*Arel_Pgp24

/(Km_Pgp_inh+fent_inh*y254/Vent24),

PSax24_inh = (PSpass_a24_inh+ PSpgp24_inh),

CL24_inh = Vmax_3A4_inh*Arel_3A4_24 /(Km_3A4_inh+fent_inh*y254/Vent24),

$$P_{\text{pass_lum_a25_inh}} = P_{\text{invivo_inh}} \frac{(1+10^{(\text{pH_Caco2}-\text{pKa_acid_inh})}+10^{(\text{pKa_base_inh}-\text{pH_Caco2})})}{(1+10^{(\text{pH_lum25}-\text{pKa_acid_inh})}}$$

$$+10^{(\text{pKa_base_inh}-\text{pH_lum25})}),$$

$$P_{\text{Spass_lum_a25_inh}} = P_{\text{pass_lum_a25_inh}} \text{ME Sent25},$$

$$P_{\text{Spass_a25_inh}} = P_{\text{invivo_inh}} \text{ME Sent25},$$

$$P_{\text{Spass_b25_inh}} = P_{\text{invivo_inh}} \text{Sent25},$$

$$P_{\text{Sap25_inh}} = P_{\text{Spass_lum_a25_inh}},$$

$$P_{\text{Sbp25_inh}} = P_{\text{Spass_b25_inh}},$$

$$P_{\text{Sbx25_inh}} = P_{\text{Spass_b25_inh}},$$

$$P_{\text{Spgp25_inh}} = \text{psf_Pgp} * V_{\text{max_Pgp_inh}} * A_{\text{rel_Pgp25}}$$

$$/(\text{Km_Pgp_inh} + \text{fent_inh} * y_{255} / V_{\text{ent25}}),$$

$$P_{\text{Sax25_inh}} = (P_{\text{Spass_a25_inh}} + P_{\text{Spgp25_inh}}),$$

$$CL_{25_inh} = V_{\text{max_3A4_inh}} * A_{\text{rel_3A4_25}} / (\text{Km_3A4_inh} + \text{fent_inh} * y_{255} / V_{\text{ent25}}),$$

$$P_{\text{pass_lum_a26_inh}} = P_{\text{invivo_inh}} \frac{(1+10^{(\text{pH_Caco2}-\text{pKa_acid_inh})}+10^{(\text{pKa_base_inh}-\text{pH_Caco2})})}{(1+10^{(\text{pH_lum26}-\text{pKa_acid_inh})}}$$

$$+10^{(\text{pKa_base_inh}-\text{pH_lum26})}),$$

$$P_{\text{Spass_lum_a26_inh}} = P_{\text{pass_lum_a26_inh}} \text{ME Sent26},$$

$$P_{\text{Spass_a26_inh}} = P_{\text{invivo_inh}} \text{ME Sent26},$$

$$P_{\text{Spass_b26_inh}} = P_{\text{invivo_inh}} \text{Sent26},$$

$$P_{\text{Sap26_inh}} = P_{\text{Spass_lum_a26_inh}},$$

$$P_{\text{Sbp26_inh}} = P_{\text{Spass_b26_inh}},$$

$$P_{\text{Sbx26_inh}} = P_{\text{Spass_b26_inh}},$$

$$P_{\text{Spgp26_inh}} = \text{psf_Pgp} * V_{\text{max_Pgp_inh}} * A_{\text{rel_Pgp26}}$$

$$/(\text{Km_Pgp_inh} + \text{fent_inh} * y_{256} / V_{\text{ent26}}),$$

$$PSax26_inh = (PSpass_a26_inh + PSpgp26_inh),$$

$$CL26_inh = Vmax_3A4_inh * Arel_3A4_26 / (Km_3A4_inh + fent_inh * y256 / Vent26),$$

$$Ppass_lum_a27_inh = P_invivo_inh (1 + 10^{(pH_Caco2 - pKa_acid_inh)} + 10^{(pKa_base_inh - pH_Caco2)}) / (1 + 10^{(pH_lum27 - pKa_acid_inh)}$$

$$+ 10^{(pKa_base_inh - pH_lum27)}),$$

$$PSpass_lum_a27_inh = Ppass_lum_a27_inh ME Sent27,$$

$$PSpass_a27_inh = P_invivo_inh ME Sent27,$$

$$PSpass_b27_inh = P_invivo_inh Sent27,$$

$$PSap27_inh = PSpass_lum_a27_inh,$$

$$PSbp27_inh = PSpass_b27_inh,$$

$$PSbx27_inh = PSpass_b27_inh,$$

$$PSpgp27_inh = psf_Pgp * Vmax_Pgp_inh * Arel_Pgp27$$

$$/ (Km_Pgp_inh + fent_inh * y257 / Vent27),$$

$$PSax27_inh = (PSpass_a27_inh + PSpgp27_inh),$$

$$CL27_inh = Vmax_3A4_inh * Arel_3A4_27 / (Km_3A4_inh + fent_inh * y257 / Vent27),$$

$$Ppass_lum_a28_inh = P_invivo_inh (1 + 10^{(pH_Caco2 - pKa_acid_inh)} + 10^{(pKa_base_inh - pH_Caco2)}) / (1 + 10^{(pH_lum28 - pKa_acid_inh)}$$

$$+ 10^{(pKa_base_inh - pH_lum28)}),$$

$$PSpass_lum_a28_inh = Ppass_lum_a28_inh ME Sent28,$$

$$PSpass_a28_inh = P_invivo_inh ME Sent28,$$

$$PSpass_b28_inh = P_invivo_inh Sent28,$$

$$PSap28_inh = PSpass_lum_a28_inh,$$

$$PSbp28_inh = PSpass_b28_inh,$$

$$PSbx28_inh = PSpass_b28_inh,$$

$$PSpgp28_inh = psf_Pgp * Vmax_Pgp_inh * Arel_Pgp28 / (Km_Pgp_inh + fent * y258 / Vent28),$$

$$PSax28_inh = (PSpass_a28_inh + PSpgp28_inh),$$

$$CL28_inh = Vmax_3A4_inh * Arel_3A4_28 / (Km_3A4_inh + fent_inh * y258 / Vent28),$$

$$Ppass_lum_a29_inh = P_invivo_inh (1 + 10^{(pH_Caco2 - pKa_acid_inh)} + 10^{(pKa_base_inh - pH_Caco2)}) / (1 + 10^{(pH_lum29 - pKa_acid_inh)} + 10^{(pKa_base_inh - pH_lum29)}),$$

$$PSpass_lum_a29_inh = Ppass_lum_a29_inh ME Sent29,$$

$$PSpass_a29_inh = P_invivo_inh ME Sent29,$$

$$PSpass_b29_inh = P_invivo_inh Sent29,$$

$$PSap29_inh = PSpass_lum_a29_inh,$$

$$PSbp29_inh = PSpass_b29_inh,$$

$$PSbx29_inh = PSpass_b29_inh,$$

$$PSpgp29_inh = psf_Pgp * Vmax_Pgp_inh * Arel_Pgp29 / (Km_Pgp_inh + fent * y259 / Vent29),$$

$$PSax29_inh = (PSpass_a29_inh + PSpgp29_inh),$$

$$CL29_inh = Vmax_3A4_inh * Arel_3A4_29 / (Km_3A4_inh + fent_inh * y259 / Vent29),$$

$$Ppass_lum_a30_inh = P_invivo_inh (1 + 10^{(pH_Caco2 - pKa_acid_inh)} + 10^{(pKa_base_inh - pH_Caco2)}) / (1 + 10^{(pH_lum30 - pKa_acid_inh)} + 10^{(pKa_base_inh - pH_lum30)}),$$

$$PSpass_lum_a30_inh = Ppass_lum_a30_inh ME Sent30,$$

$$PSpass_a30_inh = P_invivo_inh ME Sent30,$$

$$PSpass_b30_inh = P_invivo_inh Sent30,$$

$$PSap30_inh = PSpass_lum_a30_inh,$$

$$PSbp30_inh = PSpass_b30_inh,$$

$$PSbx30_inh = PSpass_b30_inh,$$

$$PSpgp30_inh = psf_Pgp * Vmax_Pgp_inh * Arel_Pgp30$$

$$/(Km_Pgp_inh + fent_inh * y260 / Vent30),$$

$$PSax30_inh = (PSpass_a30_inh + PSpgp30_inh),$$

$$CL30_inh = Vmax_3A4_inh * Arel_3A4_30 / (Km_3A4_inh + fent_inh * y260 / Vent30),$$

$$Ppass_lum_a31_inh = P_invivo_inh (1 + 10^{(pH_Caco2 - pKa_acid_inh)} + 10^{(pKa_base_inh - pH_Caco2)}) / (1 + 10^{(pH_lum31 - pKa_acid_inh)}$$

$$+ 10^{(pKa_base_inh - pH_lum31)}),$$

$$PSpass_lum_a31_inh = Ppass_lum_a31_inh ME Sent31,$$

$$PSpass_a31_inh = P_invivo_inh ME Sent31,$$

$$PSpass_b31_inh = P_invivo_inh Sent31,$$

$$PSap31_inh = PSpass_lum_a31_inh,$$

$$PSbp31_inh = PSpass_b31_inh,$$

$$PSbx31_inh = PSpass_b31_inh,$$

$$PSpgp31_inh = psf_Pgp * Vmax_Pgp_inh * Arel_Pgp31$$

$$/(Km_Pgp_inh + fent_inh * y261 / Vent31),$$

$$PSax31_inh = (PSpass_a31_inh + PSpgp31_inh),$$

$$CL31_inh = Vmax_3A4_inh * Arel_3A4_31 / (Km_3A4_inh + fent_inh * y261 / Vent31),$$

$$Ppass_lum_a32_inh = P_invivo_inh (1 + 10^{(pH_Caco2 - pKa_acid_inh)} + 10^{(pKa_base_inh - pH_Caco2)}) / (1 + 10^{(pH_lum32 - pKa_acid_inh)}$$

$$+ 10^{(pKa_base_inh - pH_lum32)}),$$

$$PSpass_lum_a32_inh = Ppass_lum_a32_inh ME Sent32,$$

$PS_{pass_a32_inh} = P_{invivo_inh} ME_{Sent32},$
 $PS_{pass_b32_inh} = P_{invivo_inh} Sent32,$
 $PS_{ap32_inh} = PS_{pass_lum_a32_inh},$
 $PS_{bp32_inh} = PS_{pass_b32_inh},$
 $PS_{bx32_inh} = PS_{pass_b32_inh},$
 $PS_{pgp32_inh} = \frac{psf_Pgp * V_{max_Pgp_inh} * A_{rel_Pgp32}}{(K_{m_Pgp_inh} + f_{ent_inh} * y_{262} / V_{ent32})},$
 $PS_{ax32_inh} = (PS_{pass_a32_inh} + PS_{pgp32_inh}),$
 $CL_{32_inh} = \frac{V_{max_3A4_inh} * A_{rel_3A4_32}}{(K_{m_3A4_inh} + f_{ent_inh} * y_{262} / V_{ent32})},$

$P_{pass_lum_a33_inh} = P_{invivo_inh} \frac{(1 + 10^{(pH_{Caco2} - pK_{a_acid_inh})} + 10^{(pK_{a_base_inh} - pH_{Caco2})})}{(1 + 10^{(pH_{lum33} - pK_{a_acid_inh})} + 10^{(pK_{a_base_inh} - pH_{lum33})}),$
 $PS_{pass_lum_a33_inh} = P_{pass_lum_a33_inh} ME_{Sent33},$
 $PS_{pass_a33_inh} = P_{invivo_inh} ME_{Sent33},$
 $PS_{pass_b33_inh} = P_{invivo_inh} Sent33,$
 $PS_{ap33_inh} = PS_{pass_lum_a33_inh},$
 $PS_{bp33_inh} = PS_{pass_b33_inh},$
 $PS_{bx33_inh} = PS_{pass_b33_inh},$
 $PS_{pgp33_inh} = \frac{psf_Pgp * V_{max_Pgp_inh} * A_{rel_Pgp33}}{(K_{m_Pgp_inh} + f_{ent_inh} * y_{263} / V_{ent33})},$
 $PS_{ax33_inh} = (PS_{pass_a33_inh} + PS_{pgp33_inh}),$
 $CL_{33_inh} = \frac{V_{max_3A4_inh} * A_{rel_3A4_33}}{(K_{m_3A4_inh} + f_{ent_inh} * y_{263} / V_{ent33})},$

$$P_{\text{pass_lum_a34_inh}} = P_{\text{invivo_inh}} \frac{(1+10^{(\text{pH_Caco2}-\text{pKa_acid_inh})}+10^{(\text{pKa_base_inh}-\text{pH_Caco2}))}}{(1+10^{(\text{pH_lum34}-\text{pKa_acid_inh})}}$$

$$+10^{(\text{pKa_base_inh}-\text{pH_lum34}))},$$

$$P_{\text{Spass_lum_a34_inh}} = P_{\text{pass_lum_a34_inh}} \text{ ME Sent34},$$

$$P_{\text{Spass_a34_inh}} = P_{\text{invivo_inh}} \text{ ME Sent34},$$

$$P_{\text{Spass_b34_inh}} = P_{\text{invivo_inh}} \text{ Sent34},$$

$$P_{\text{Sap34_inh}} = P_{\text{Spass_lum_a34_inh}},$$

$$P_{\text{Sbp34_inh}} = P_{\text{Spass_b34_inh}},$$

$$P_{\text{Sbx34_inh}} = P_{\text{Spass_b34_inh}},$$

$$P_{\text{Spgp34_inh}} = \text{psf_Pgp} * V_{\text{max_Pgp_inh}} * A_{\text{rel_Pgp34}}$$

$$/(\text{Km_Pgp_inh} + \text{fent_inh} * y_{264} / V_{\text{ent34}}),$$

$$P_{\text{Sax34_inh}} = (P_{\text{Spass_a34_inh}} + P_{\text{Spgp34_inh}}),$$

$$CL_{34_inh} = V_{\text{max_3A4_inh}} * A_{\text{rel_3A4_34}} / (\text{Km_3A4_inh} + \text{fent_inh} * y_{264} / V_{\text{ent34}}),$$

$$P_{\text{pass_lum_a35_inh}} = P_{\text{invivo_inh}} \frac{(1+10^{(\text{pH_Caco2}-\text{pKa_acid_inh})}+10^{(\text{pKa_base_inh}-\text{pH_Caco2}))}}{(1+10^{(\text{pH_lum35}-\text{pKa_acid_inh})}}$$

$$+10^{(\text{pKa_base_inh}-\text{pH_lum35}))},$$

$$P_{\text{Spass_lum_a35_inh}} = P_{\text{pass_lum_a35_inh}} \text{ ME Sent35},$$

$$P_{\text{Spass_a35_inh}} = P_{\text{invivo_inh}} \text{ ME Sent35},$$

$$P_{\text{Spass_b35_inh}} = P_{\text{invivo_inh}} \text{ Sent35},$$

$$P_{\text{Sap35_inh}} = P_{\text{Spass_lum_a35_inh}},$$

$$P_{\text{Sbp35_inh}} = P_{\text{Spass_b35_inh}},$$

$$P_{\text{Sbx35_inh}} = P_{\text{Spass_b35_inh}},$$

$$P_{\text{Spgp35_inh}} = \text{psf_Pgp} * V_{\text{max_Pgp_inh}} * A_{\text{rel_Pgp35}}$$

$$/(\text{Km_Pgp_inh} + \text{fent_inh} * y_{265} / V_{\text{ent35}}),$$

$$PSax35_inh = (PSpass_a35_inh + PSpgp35_inh),$$

$$CL35_inh = Vmax_3A4_inh * Arel_3A4_35 / (Km_3A4_inh + fent_inh * y265 / Vent35),$$

$$Ppass_lum_a36_inh = P_invivo_inh \frac{(1 + 10^{(pH_Caco2 - pKa_acid_inh)} + 10^{(pKa_base_inh - pH_Caco2)})}{(1 + 10^{(pH_lum36 - pKa_acid_inh)}$$

$$+ 10^{(pKa_base_inh - pH_lum36)}),$$

$$PSpass_lum_a36_inh = Ppass_lum_a36_inh ME Sent36,$$

$$PSpass_a36_inh = P_invivo_inh ME Sent36,$$

$$PSpass_b36_inh = P_invivo_inh Sent36,$$

$$PSap36_inh = PSpass_lum_a36_inh,$$

$$PSbp36_inh = PSpass_b36_inh,$$

$$PSbx36_inh = PSpass_b36_inh,$$

$$PSpgp36_inh = psf_Pgp * Vmax_Pgp_inh * Arel_Pgp36$$

$$/ (Km_Pgp_inh + fent_inh * y266 / Vent36),$$

$$PSax36_inh = (PSpass_a36_inh + PSpgp36_inh),$$

$$CL36_inh = Vmax_3A4_inh * Arel_3A4_36 / (Km_3A4_inh + fent_inh * y266 / Vent36),$$

$$Ppass_lum_a37_inh = P_invivo_inh \frac{(1 + 10^{(pH_Caco2 - pKa_acid_inh)} + 10^{(pKa_base_inh - pH_Caco2)})}{(1 + 10^{(pH_lum37 - pKa_acid_inh)}$$

$$+ 10^{(pKa_base_inh - pH_lum37)}),$$

$$PSpass_lum_a37_inh = Ppass_lum_a37_inh ME Sent37,$$

$$PSpass_a37_inh = P_invivo_inh ME Sent37,$$

$$PSpass_b37_inh = P_invivo_inh Sent37,$$

$$PSap37_inh = PSpass_lum_a37_inh,$$

$$PSbp37_inh = PSpass_b37_inh,$$

PSbx37_inh = PSpass_b37_inh,

PSpgp37_inh = psf_Pgp*Vmax_Pgp_inh*Arel_Pgp37

/(Km_Pgp_inh+fent_inh*y267/Vent37),

PSax37_inh = (PSpass_a37_inh+ PSpgp37_inh),

CL37_inh = Vmax_3A4_inh*Arel_3A4_37/(Km_3A4_inh+fent_inh*y267/Vent37),

Ppass_lum_a38_inh = P_invivo_inh (1+10^(pH_Caco2-pKa_acid_inh)+10^(pKa_base_inh-

pH_Caco2))/(1+10^(pH_lum38-pKa_acid_inh)

+10^(pKa_base_inh-pH_lum38)),

PSpass_lum_a38_inh= Ppass_lum_a38_inh ME Sent38,

PSpass_a38_inh = P_invivo_inh ME Sent38,

PSpass_b38_inh = P_invivo_inh Sent38,

PSap38_inh = PSpass_lum_a38_inh,

PSbp38_inh = PSpass_b38_inh,

PSbx38_inh = PSpass_b38_inh,

PSpgp38_inh = psf_Pgp*Vmax_Pgp_inh*Arel_Pgp38

/(Km_Pgp_inh+fent_inh*y268/Vent38),

PSax38_inh = (PSpass_a38_inh+ PSpgp38_inh),

CL38_inh = Vmax_3A4_inh*Arel_3A4_38/(Km_3A4_inh+fent_inh*y268/Vent38),

Ppass_lum_a39_inh = P_invivo_inh (1+10^(pH_Caco2-pKa_acid_inh)+10^(pKa_base_inh-

pH_Caco2))/(1+10^(pH_lum39-pKa_acid_inh)

+10^(pKa_base_inh-pH_lum39)),

PSpass_lum_a39_inh= Ppass_lum_a39_inh ME Sent39,

PSpass_a39_inh = P_invivo_inh ME Sent39,

PSpass_b39_inh = P_invivo_inh Sent39,

PSap39_inh = PSpass_lum_a39_inh,

PSbp39_inh = PSpass_b39_inh,

PSbx39_inh = PSpass_b39_inh,

PSpgp39_inh = psf_Pgp*Vmax_Pgp_inh*Arel_Pgp39

/(Km_Pgp_inh+fent_inh*y269/Vent39),

PSax39_inh = (PSpass_a39_inh+ PSpgp39_inh),

CL39_inh = Vmax_3A4_inh*Arel_3A4_39/(Km_3A4_inh+fent_inh*y269/Vent39),

Ppass_lum_a40_inh = P_invivo_inh (1+10^(pH_Caco2-pKa_acid_inh)+10^(pKa_base_inh-
pH_Caco2))/(1+10^(pH_lum40-pKa_acid_inh)
+10^(pKa_base_inh-pH_lum40)),

PSpass_lum_a40_inh= Ppass_lum_a40_inh ME Sent40,

PSpass_a40_inh = P_invivo_inh ME Sent40,

PSpass_b40_inh = P_invivo_inh Sent40,

PSap40_inh = PSpass_lum_a40_inh,

PSbp40_inh = PSpass_b40_inh,

PSbx40_inh = PSpass_b40_inh,

PSpgp40_inh = psf_Pgp*Vmax_Pgp_inh*Arel_Pgp40

/(Km_Pgp_inh+fent_inh*y270/Vent40),

PSax40_inh = (PSpass_a40_inh+ PSpgp40_inh),

CL40_inh = Vmax_3A4_inh*Arel_3A4_40/(Km_3A4_inh+fent_inh*y270/Vent40),

; Drug concentration in the lumen

$y_{191}' = (kg * y_{313}) * V_g \text{ div} / V + c_{3a_1} * y_{191} + c_{4a_2} * y_{192} + c_{5_3} * y_{193} -$
 $PSap1_inh * y_{191} / y_1 + PSax1_inh * fent_inh * y_{231} / Vent1 / (V / \text{div}),$
 if $y_{191} < 0$ then $y_{191} = 0$ endif,
 $y_{192}' = c_{2a_1} * y_{191} + c_{3_2} * y_{192} + c_{4_3} * y_{193} + c_{5_4} * y_{194} -$
 $PSap2_inh * y_{192} / y_2 + PSax2_inh * fent_inh * y_{232} / Vent2 / (V / \text{div}),$
 if $y_{192} < 0$ then $y_{192} = 0$ endif,
 $y_{193}' = c_{1_1} * y_{191} + c_{2_2} * y_{192} + c_{3_3} * y_{193} + c_{4_4} * y_{194} + c_{5_5} * y_{195} -$
 $PSap3_inh * y_{193} / y_3 + PSax3_inh * fent_inh * y_{233} / Vent3 / (V / \text{div}),$
 if $y_{193} < 0$ then $y_{193} = 0$ endif,
 $y_{194}' = c_{1_2} * y_{192} + c_{2_3} * y_{193} + c_{3_4} * y_{194} + c_{4_5} * y_{195} + c_{5_6} * y_{196} -$
 $PSap4_inh * y_{194} / y_4 + PSax4_inh * fent_inh * y_{234} / Vent4 / (V / \text{div}),$
 if $y_{194} < 0$ then $y_{194} = 0$ endif,
 $y_{195}' = c_{1_3} * y_{193} + c_{2_4} * y_{194} + c_{3_5} * y_{195} + c_{4_6} * y_{196} + c_{5_7} * y_{197} -$
 $PSap5_inh * y_{195} / y_5 + PSax5_inh * fent_inh * y_{235} / Vent5 / (V / \text{div}),$
 if $y_{195} < 0$ then $y_{195} = 0$ endif,
 $y_{196}' = c_{1_4} * y_{194} + c_{2_5} * y_{195} + c_{3_6} * y_{196} + c_{4_7} * y_{197} + c_{5_8} * y_{198} -$
 $PSap6_inh * y_{196} / y_6 + PSax6_inh * fent_inh * y_{236} / Vent6 / (V / \text{div}),$
 if $y_{196} < 0$ then $y_{196} = 0$ endif,
 $y_{197}' = c_{1_5} * y_{195} + c_{2_6} * y_{196} + c_{3_7} * y_{197} + c_{4_8} * y_{198} + c_{5_9} * y_{199} -$
 $PSap7_inh * y_{197} / y_7 + PSax7_inh * fent_inh * y_{237} / Vent7 / (V / \text{div}),$
 if $y_{197} < 0$ then $y_{197} = 0$ endif,
 $y_{198}' = c_{1_6} * y_{196} + c_{2_7} * y_{197} + c_{3_8} * y_{198} + c_{4_9} * y_{199} + c_{5_10} * y_{200} -$
 $PSap8_inh * y_{198} / y_8 + PSax8_inh * fent_inh * y_{238} / Vent8 / (V / \text{div}),$
 if $y_{198} < 0$ then $y_{198} = 0$ endif,

$y_{199}' = c_{1_7} * y_{197} + c_{2_8} * y_{198} + c_{3_9} * y_{199} + c_{4_10} * y_{200} + c_{5_11} * y_{201} -$
 $PSap9_inh * y_{199} / y_9 + PSax9_inh * fent_inh * y_{239} / Vent9 / (V/div),$
 if $y_{199} < 0$ then $y_{199} = 0$ endif,

$y_{200}' = c_{1_8} * y_{198} + c_{2_9} * y_{199} + c_{3_10} * y_{200} + c_{4_11} * y_{201} + c_{5_12} * y_{202} -$
 $PSap10_inh * y_{200} / y_{10} + PSax10_inh * fent_inh * y_{240} / Vent10 / (V/div),$
 if $y_{200} < 0$ then $y_{200} = 0$ endif,

$y_{201}' = c_{1_9} * y_{199} + c_{2_10} * y_{200} + c_{3_11} * y_{201} + c_{4_12} * y_{202} + c_{5_13} * y_{203} -$
 $PSap11_inh * y_{201} / y_{11} + PSax11_inh * fent_inh * y_{241} / Vent11 / (V/div),$
 if $y_{201} < 0$ then $y_{201} = 0$ endif,

$y_{202}' = c_{1_10} * y_{200} + c_{2_11} * y_{201} + c_{3_12} * y_{202} + c_{4_13} * y_{203} + c_{5_14} * y_{204} -$
 $PSap12_inh * y_{202} / y_{12} + PSax12_inh * fent_inh * y_{242} / Vent12 / (V/div),$
 if $y_{202} < 0$ then $y_{202} = 0$ endif,

$y_{203}' = c_{1_11} * y_{201} + c_{2_12} * y_{202} + c_{3_13} * y_{203} + c_{4_14} * y_{204} + c_{5_15} * y_{205} -$
 $PSap13_inh * y_{203} / y_{13} + PSax13_inh * fent_inh * y_{243} / Vent13 / (V/div),$
 if $y_{203} < 0$ then $y_{203} = 0$ endif,

$y_{204}' = c_{1_12} * y_{202} + c_{2_13} * y_{203} + c_{3_14} * y_{204} + c_{4_15} * y_{205} + c_{5_16} * y_{206} -$
 $PSap14_inh * y_{204} / y_{14} + PSax14_inh * fent_inh * y_{244} / Vent14 / (V/div),$
 if $y_{204} < 0$ then $y_{204} = 0$ endif,

$y_{205}' = c_{1_13} * y_{203} + c_{2_14} * y_{204} + c_{3_15} * y_{205} + c_{4_16} * y_{206} + c_{5_17} * y_{207} -$
 $PSap15_inh * y_{205} / y_{15} + PSax15_inh * fent_inh * y_{245} / Vent15 / (V/div),$
 if $y_{205} < 0$ then $y_{205} = 0$ endif,

$y_{206}' = c_{1_14} * y_{204} + c_{2_15} * y_{205} + c_{3_16} * y_{206} + c_{4_17} * y_{207} + c_{5_18} * y_{208} -$
 $PSap16_inh * y_{206} / y_{16} + PSax16_inh * fent_inh * y_{246} / Vent16 / (V/div),$
 if $y_{206} < 0$ then $y_{206} = 0$ endif,

$y_{207}' = c_{1_15} * y_{205} + c_{2_16} * y_{206} + c_{3_17} * y_{207} + c_{4_18} * y_{208} + c_{5_19} * y_{209} -$
 $PSap_{17_inh} * y_{207} / y_{17} + PSax_{17_inh} * fent_inh * y_{247} / Vent_{17} / (V / div),$
 if $y_{207} < 0$ then $y_{207} = 0$ endif,

$y_{208}' = c_{1_16} * y_{206} + c_{2_17} * y_{207} + c_{3_18} * y_{208} + c_{4_19} * y_{209} + c_{5_20} * y_{210} -$
 $PSap_{18_inh} * y_{208} / y_{18} + PSax_{18_inh} * fent_inh * y_{248} / Vent_{18} / (V / div),$
 if $y_{208} < 0$ then $y_{208} = 0$ endif,

$y_{209}' = c_{1_17} * y_{207} + c_{2_18} * y_{208} + c_{3_19} * y_{209} + c_{4_20} * y_{210} + c_{5_21} * y_{211} -$
 $PSap_{19_inh} * y_{209} / y_{19} + PSax_{19_inh} * fent_inh * y_{249} / Vent_{19} / (V / div),$
 if $y_{209} < 0$ then $y_{209} = 0$ endif,

$y_{210}' = c_{1_18} * y_{208} + c_{2_19} * y_{209} + c_{3_20} * y_{210} + c_{4_21} * y_{211} + c_{5_22} * y_{212} -$
 $PSap_{20_inh} * y_{210} / y_{20} + PSax_{20_inh} * fent_inh * y_{250} / Vent_{20} / (V / div),$
 if $y_{210} < 0$ then $y_{210} = 0$ endif,

$y_{211}' = c_{1_19} * y_{209} + c_{2_20} * y_{210} + c_{3_21} * y_{211} + c_{4_22} * y_{212} + c_{5_23} * y_{213} -$
 $PSap_{21_inh} * y_{211} / y_{21} + PSax_{21_inh} * fent_inh * y_{251} / Vent_{21} / (V / div),$
 if $y_{211} < 0$ then $y_{211} = 0$ endif,

$y_{212}' = c_{1_20} * y_{210} + c_{2_21} * y_{211} + c_{3_22} * y_{212} + c_{4_23} * y_{213} + c_{5_24} * y_{214} -$
 $PSap_{22_inh} * y_{212} / y_{22} + PSax_{22_inh} * fent_inh * y_{252} / Vent_{22} / (V / div),$
 if $y_{212} < 0$ then $y_{212} = 0$ endif,

$y_{213}' = c_{1_21} * y_{211} + c_{2_22} * y_{212} + c_{3_23} * y_{213} + c_{4_24} * y_{214} + c_{5_25} * y_{215} -$
 $PSap_{23_inh} * y_{213} / y_{23} + PSax_{23_inh} * fent_inh * y_{253} / Vent_{23} / (V / div),$
 if $y_{213} < 0$ then $y_{213} = 0$ endif,

$y_{214}' = c_{1_22} * y_{212} + c_{2_23} * y_{213} + c_{3_24} * y_{214} + c_{4_25} * y_{215} + c_{5_26} * y_{216} -$
 $PSap_{24_inh} * y_{214} / y_{24} + PSax_{24_inh} * fent_inh * y_{254} / Vent_{24} / (V / div),$
 if $y_{214} < 0$ then $y_{214} = 0$ endif,

$y_{215}' = c_{1_23} * y_{213} + c_{2_24} * y_{214} + c_{3_25} * y_{215} + c_{4_26} * y_{216} + c_{5_27} * y_{217} -$
 $PSap_{25_inh} * y_{215} / y_{25} + PSax_{25_inh} * fent_inh * y_{255} / Vent_{25} / (V / div),$
 if $y_{215} < 0$ then $y_{215} = 0$ endif,

$y_{216}' = c_{1_24} * y_{214} + c_{2_25} * y_{215} + c_{3_26} * y_{216} + c_{4_27} * y_{217} + c_{5_28} * y_{218} -$
 $PSap_{26_inh} * y_{216} / y_{26} + PSax_{26_inh} * fent_inh * y_{256} / Vent_{26} / (V / div),$
 if $y_{216} < 0$ then $y_{216} = 0$ endif,

$y_{217}' = c_{1_25} * y_{215} + c_{2_26} * y_{216} + c_{3_27} * y_{217} + c_{4_28} * y_{218} + c_{5_29} * y_{219} -$
 $PSap_{27_inh} * y_{217} / y_{27} + PSax_{27_inh} * fent_inh * y_{257} / Vent_{27} / (V / div),$
 if $y_{217} < 0$ then $y_{217} = 0$ endif,

$y_{218}' = c_{1_26} * y_{216} + c_{2_27} * y_{217} + c_{3_28} * y_{218} + c_{4_29} * y_{219} + c_{5_30} * y_{220} -$
 $PSap_{28_inh} * y_{218} / y_{28} + PSax_{28_inh} * fent_inh * y_{258} / Vent_{28} / (V / div),$
 if $y_{218} < 0$ then $y_{218} = 0$ endif,

$y_{219}' = c_{1_27} * y_{217} + c_{2_28} * y_{218} + c_{3_29} * y_{219} + c_{4_30} * y_{220} + c_{5_31} * y_{221} -$
 $PSap_{29_inh} * y_{219} / y_{29} + PSax_{29_inh} * fent_inh * y_{259} / Vent_{29} / (V / div),$
 if $y_{219} < 0$ then $y_{219} = 0$ endif,

$y_{220}' = c_{1_28} * y_{218} + c_{2_29} * y_{219} + c_{3_30} * y_{220} + c_{4_31} * y_{221} + c_{5_32} * y_{222} -$
 $PSap_{30_inh} * y_{220} / y_{30} + PSax_{30_inh} * fent_inh * y_{260} / Vent_{30} / (V / div),$
 if $y_{220} < 0$ then $y_{220} = 0$ endif,

$y_{221}' = c_{1_29} * y_{219} + c_{2_30} * y_{220} + c_{3_31} * y_{221} + c_{4_32} * y_{222} + c_{5_33} * y_{223} -$
 $PSap_{31_inh} * y_{221} / y_{31} + PSax_{31_inh} * fent_inh * y_{261} / Vent_{31} / (V / div),$
 if $y_{221} < 0$ then $y_{221} = 0$ endif,

$y_{222}' = c_{1_30} * y_{220} + c_{2_31} * y_{221} + c_{3_32} * y_{222} + c_{4_33} * y_{223} + c_{5_34} * y_{224} -$
 $PSap_{32_inh} * y_{222} / y_{32} + PSax_{32_inh} * fent_inh * y_{262} / Vent_{32} / (V / div),$
 if $y_{222} < 0$ then $y_{222} = 0$ endif,

$y_{223}' = c_{1_31} * y_{221} + c_{2_32} * y_{222} + c_{3_33} * y_{223} + c_{4_34} * y_{224} + c_{5_35} * y_{225} -$
 $PSap_{33_inh} * y_{223} / y_{33} + PSax_{33_inh} * fent_inh * y_{263} / Vent_{33} / (V / div),$
 if $y_{223} < 0$ then $y_{223} = 0$ endif,

$y_{224}' = c_{1_32} * y_{222} + c_{2_33} * y_{223} + c_{3_34} * y_{224} + c_{4_35} * y_{225} + c_{5_36} * y_{226} -$
 $PSap_{34_inh} * y_{224} / y_{34} + PSax_{34_inh} * fent_inh * y_{264} / Vent_{34} / (V / div),$
 if $y_{224} < 0$ then $y_{224} = 0$ endif,

$y_{225}' = c_{1_33} * y_{223} + c_{2_34} * y_{224} + c_{3_35} * y_{225} + c_{4_36} * y_{226} + c_{5_37} * y_{227} -$
 $PSap_{35_inh} * y_{225} / y_{35} + PSax_{35_inh} * fent_inh * y_{265} / Vent_{35} / (V / div),$
 if $y_{225} < 0$ then $y_{225} = 0$ endif,

$y_{226}' = c_{1_34} * y_{224} + c_{2_35} * y_{225} + c_{3_36} * y_{226} + c_{4_37} * y_{227} + c_{5_38} * y_{228} -$
 $PSap_{36_inh} * y_{226} / y_{36} + PSax_{36_inh} * fent_inh * y_{266} / Vent_{36} / (V / div),$
 if $y_{226} < 0$ then $y_{226} = 0$ endif,

$y_{227}' = c_{1_35} * y_{225} + c_{2_36} * y_{226} + c_{3_37} * y_{227} + c_{4_38} * y_{228} + c_{5_39} * y_{229} -$
 $PSap_{37_inh} * y_{227} / y_{37} + PSax_{37_inh} * fent_inh * y_{267} / Vent_{37} / (V / div),$
 if $y_{227} < 0$ then $y_{227} = 0$ endif,

$y_{228}' = c_{1_36} * y_{226} + c_{2_37} * y_{227} + c_{3_38} * y_{228} + c_{4_39} * y_{229} + c_{5_40} * y_{230} -$
 $PSap_{38_inh} * y_{228} / y_{38} + PSax_{38_inh} * fent_inh * y_{268} / Vent_{38} / (V / div),$
 if $y_{228} < 0$ then $y_{228} = 0$ endif,

$y_{229}' = c_{1_37} * y_{227} + c_{2_38} * y_{228} + c_{3_39} * y_{229} + c_{4a_40} * y_{230} -$
 $PSap_{39_inh} * y_{229} / y_{39} + PSax_{39_inh} * fent_inh * y_{269} / Vent_{39} / (V / div),$
 if $y_{229} < 0$ then $y_{229} = 0$ endif,

$y_{230}' = c_{1_38} * y_{228} + c_{2b_39} * y_{229} + c_{3b_40} * y_{230} -$
 $PSap_{40_inh} * y_{230} / y_{40} + PSax_{40_inh} * fent_inh * y_{270} / Vent_{40} / (V / div),$
 if $y_{230} < 0$ then $y_{230} = 0$ endif,

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$y_{231}' = PS_{ap1_inh} * y_{191} * (V/div) / y_1 -$

$(PS_{ax1_inh} + CL_{1_inh} + PS_{bp1_inh}) * fent_inh * y_{231} / Vent_1 + PS_{bx1_inh} * y_{271} / V_{lam1},$

if $y_{231} < 0$ then $y_{231} = 0$ endif,

$y_{232}' = PS_{ap2_inh} * y_{192} * (V/div) / y_2 -$

$(PS_{ax2_inh} + CL_{2_inh} + PS_{bp2_inh}) * fent_inh * y_{232} / Vent_2 + PS_{bx2_inh} * y_{272} / V_{lam2},$

if $y_{232} < 0$ then $y_{232} = 0$ endif,

$y_{233}' = PS_{ap3_inh} * y_{193} * (V/div) / y_3 -$

$(PS_{ax3_inh} + CL_{3_inh} + PS_{bp3_inh}) * fent_inh * y_{233} / Vent_3 + PS_{bx3_inh} * y_{273} / V_{lam3},$

if $y_{233} < 0$ then $y_{233} = 0$ endif,

$y_{234}' = PS_{ap4_inh} * y_{194} * (V/div) / y_4 -$

$(PS_{ax4_inh} + CL_{4_inh} + PS_{bp4_inh}) * fent_inh * y_{234} / Vent_4 + PS_{bx4_inh} * y_{274} / V_{lam4},$

if $y_{234} < 0$ then $y_{234} = 0$ endif,

$y_{235}' = PS_{ap5_inh} * y_{195} * (V/div) / y_5 -$

$(PS_{ax5_inh} + CL_{5_inh} + PS_{bp5_inh}) * fent_inh * y_{235} / Vent_5 + PS_{bx5_inh} * y_{275} / V_{lam5},$

if $y_{235} < 0$ then $y_{235} = 0$ endif,

$y_{236}' = PS_{ap6_inh} * y_{196} * (V/div) / y_6 -$

$(PS_{ax6_inh} + CL_{6_inh} + PS_{bp6_inh}) * fent_inh * y_{236} / Vent_6 + PS_{bx6_inh} * y_{276} / V_{lam6},$

if $y_{236} < 0$ then $y_{236} = 0$ endif,

$y_{237}' = PS_{ap7_inh} * y_{197} * (V/div) / y_7 -$

$(PS_{ax7_inh} + CL_{7_inh} + PS_{bp7_inh}) * fent_inh * y_{237} / Vent_7 + PS_{bx7_inh} * y_{277} / V_{lam7},$

if $y_{237} < 0$ then $y_{237} = 0$ endif,

$y_{238}' = PS_{ap8_inh} * y_{198} * (V/div) / y_8 -$

$(PS_{ax8_inh} + CL_{8_inh} + PS_{bp8_inh}) * fent_inh * y_{238} / Vent_8 + PS_{bx8_inh} * y_{278} / V_{lam8},$

if $y_{238} < 0$ then $y_{238} = 0$ endif,

$y_{239} = PS_{ap9_inh} * y_{199} * (V/div) / y_9 -$
 $(PS_{ax9_inh} + CL_{9_inh} + PS_{bp9_inh}) * fent_inh * y_{239} / Vent_9 + PS_{bx9_inh} * y_{279} / Vlam_9,$
 if $y_{239} < 0$ then $y_{239} = 0$ endif,
 $y_{240} = PS_{ap10_inh} * y_{200} * (V/div) / y_{10} -$
 $(PS_{ax10_inh} + CL_{10_inh} + PS_{bp10_inh}) * fent_inh * y_{240} / Vent_{10} + PS_{bx10_inh} * y_{280} / Vlam_{10},$
 if $y_{240} < 0$ then $y_{240} = 0$ endif,
 $y_{241} = PS_{ap11_inh} * y_{201} * (V/div) / y_{11} -$
 $(PS_{ax11_inh} + CL_{11_inh} + PS_{bp11_inh}) * fent_inh * y_{241} / Vent_{11} + PS_{bx11_inh} * y_{281} / Vlam_{11},$
 if $y_{241} < 0$ then $y_{241} = 0$ endif,
 $y_{242} = PS_{ap12_inh} * y_{202} * (V/div) / y_{12} -$
 $(PS_{ax12_inh} + CL_{12_inh} + PS_{bp12_inh}) * fent_inh * y_{242} / Vent_{12} + PS_{bx12_inh} * y_{282} / Vlam_{12},$
 if $y_{242} < 0$ then $y_{242} = 0$ endif,
 $y_{243} = PS_{ap13_inh} * y_{203} * (V/div) / y_{13} -$
 $(PS_{ax13_inh} + CL_{13_inh} + PS_{bp13_inh}) * fent_inh * y_{243} / Vent_{13} + PS_{bx13_inh} * y_{283} / Vlam_{13},$
 if $y_{243} < 0$ then $y_{243} = 0$ endif,
 $y_{244} = PS_{ap14_inh} * y_{204} * (V/div) / y_{14} -$
 $(PS_{ax14_inh} + CL_{14_inh} + PS_{bp14_inh}) * fent_inh * y_{244} / Vent_{14} + PS_{bx14_inh} * y_{284} / Vlam_{14},$
 if $y_{244} < 0$ then $y_{244} = 0$ endif,
 $y_{245} = PS_{ap15_inh} * y_{205} * (V/div) / y_{15} -$
 $(PS_{ax15_inh} + CL_{15_inh} + PS_{bp15_inh}) * fent_inh * y_{245} / Vent_{15} + PS_{bx15_inh} * y_{285} / Vlam_{15},$
 if $y_{245} < 0$ then $y_{245} = 0$ endif,
 $y_{246} = PS_{ap16_inh} * y_{206} * (V/div) / y_{16} -$
 $(PS_{ax16_inh} + CL_{16_inh} + PS_{bp16_inh}) * fent_inh * y_{246} / Vent_{16} + PS_{bx16_inh} * y_{286} / Vlam_{16},$
 if $y_{246} < 0$ then $y_{246} = 0$ endif,

$y_{247} = PS_{ap17_inh} * y_{207} * (V/div) / y_{17} -$
 $(PS_{ax17_inh} + CL_{17_inh} + PS_{bp17_inh}) * f_{ent_inh} * y_{247} / Vent_{17} + PS_{bx17_inh} * y_{287} / V_{lam17},$
 if $y_{247} < 0$ then $y_{247} = 0$ endif,

$y_{248} = PS_{ap18_inh} * y_{208} * (V/div) / y_{18} -$
 $(PS_{ax18_inh} + CL_{18_inh} + PS_{bp18_inh}) * f_{ent_inh} * y_{248} / Vent_{18} + PS_{bx18_inh} * y_{288} / V_{lam18},$
 if $y_{248} < 0$ then $y_{248} = 0$ endif,

$y_{249} = PS_{ap19_inh} * y_{209} * (V/div) / y_{19} -$
 $(PS_{ax19_inh} + CL_{19_inh} + PS_{bp19_inh}) * f_{ent_inh} * y_{249} / Vent_{19} + PS_{bx19_inh} * y_{289} / V_{lam19},$
 if $y_{249} < 0$ then $y_{249} = 0$ endif,

$y_{250} = PS_{ap20_inh} * y_{210} * (V/div) / y_{20} -$
 $(PS_{ax20_inh} + CL_{20_inh} + PS_{bp20_inh}) * f_{ent_inh} * y_{250} / Vent_{20} + PS_{bx20_inh} * y_{290} / V_{lam20},$
 if $y_{250} < 0$ then $y_{250} = 0$ endif,

$y_{251} = PS_{ap21_inh} * y_{211} * (V/div) / y_{21} -$
 $(PS_{ax21_inh} + CL_{21_inh} + PS_{bp21_inh}) * f_{ent_inh} * y_{251} / Vent_{21} + PS_{bx21_inh} * y_{291} / V_{lam21},$
 if $y_{251} < 0$ then $y_{251} = 0$ endif,

$y_{252} = PS_{ap22_inh} * y_{212} * (V/div) / y_{22} -$
 $(PS_{ax22_inh} + CL_{22_inh} + PS_{bp22_inh}) * f_{ent_inh} * y_{252} / Vent_{22} + PS_{bx22_inh} * y_{292} / V_{lam22},$
 if $y_{252} < 0$ then $y_{252} = 0$ endif,

$y_{253} = PS_{ap23_inh} * y_{213} * (V/div) / y_{23} -$
 $(PS_{ax23_inh} + CL_{23_inh} + PS_{bp23_inh}) * f_{ent_inh} * y_{253} / Vent_{23} + PS_{bx23_inh} * y_{293} / V_{lam23},$
 if $y_{253} < 0$ then $y_{253} = 0$ endif,

$y_{254} = PS_{ap24_inh} * y_{214} * (V/div) / y_{24} -$
 $(PS_{ax24_inh} + CL_{24_inh} + PS_{bp24_inh}) * f_{ent_inh} * y_{254} / Vent_{24} + PS_{bx24_inh} * y_{294} / V_{lam24},$
 if $y_{254} < 0$ then $y_{254} = 0$ endif,

$y255 = PSap25_inh * y215 * (V/div) / y25 -$
 $(PSax25_inh + CL25_inh + PSbp25_inh) * fent_inh * y255 / Vent25 + PSbx25_inh * y295 / Vlam25,$
 if $y255 < 0$ then $y255 = 0$ endif,
 $y256 = PSap26_inh * y216 * (V/div) / y26 -$
 $(PSax26_inh + CL26_inh + PSbp26_inh) * fent_inh * y256 / Vent26 + PSbx26_inh * y296 / Vlam26,$
 if $y256 < 0$ then $y256 = 0$ endif,
 $y257 = PSap27_inh * y217 * (V/div) / y27 -$
 $(PSax27_inh + CL27_inh + PSbp27_inh) * fent_inh * y257 / Vent27 + PSbx27_inh * y297 / Vlam27,$
 if $y257 < 0$ then $y257 = 0$ endif,
 $y258 = PSap28_inh * y218 * (V/div) / y28 -$
 $(PSax28_inh + CL28_inh + PSbp28_inh) * fent_inh * y258 / Vent28 + PSbx28_inh * y298 / Vlam28,$
 if $y258 < 0$ then $y258 = 0$ endif,
 $y259 = PSap29_inh * y219 * (V/div) / y29 -$
 $(PSax29_inh + CL29_inh + PSbp29_inh) * fent_inh * y259 / Vent29 + PSbx29_inh * y299 / Vlam29,$
 if $y259 < 0$ then $y259 = 0$ endif,
 $y260 = PSap30_inh * y220 * (V/div) / y30 -$
 $(PSax30_inh + CL30_inh + PSbp30_inh) * fent_inh * y260 / Vent30 + PSbx30_inh * y300 / Vlam30,$
 if $y260 < 0$ then $y260 = 0$ endif,
 $y261 = PSap31_inh * y221 * (V/div) / y31 -$
 $(PSax31_inh + CL31_inh + PSbp31_inh) * fent_inh * y261 / Vent31 + PSbx31_inh * y301 / Vlam31,$
 if $y261 < 0$ then $y261 = 0$ endif,
 $y262 = PSap32_inh * y222 * (V/div) / y32 -$
 $(PSax32_inh + CL32_inh + PSbp32_inh) * fent_inh * y262 / Vent32 + PSbx32_inh * y302 / Vlam32,$
 if $y262 < 0$ then $y262 = 0$ endif,

$y_{263} = PS_{ap33_inh} * y_{223} * (V/div) / y_{33}$
 $(PS_{ax33_inh} + CL_{33_inh} + PS_{bp33_inh}) * f_{ent_inh} * y_{263} / Vent_{33} + PS_{bx33_inh} * y_{303} / V_{lam33}$,
 if $y_{263} < 0$ then $y_{263} = 0$ endif,
 $y_{264} = PS_{ap34_inh} * y_{224} * (V/div) / y_{34}$
 $(PS_{ax34_inh} + CL_{34_inh} + PS_{bp34_inh}) * f_{ent_inh} * y_{264} / Vent_{34} + PS_{bx34_inh} * y_{304} / V_{lam34}$,
 if $y_{264} < 0$ then $y_{264} = 0$ endif,
 $y_{265} = PS_{ap35_inh} * y_{225} * (V/div) / y_{35}$
 $(PS_{ax35_inh} + CL_{35_inh} + PS_{bp35_inh}) * f_{ent_inh} * y_{265} / Vent_{35} + PS_{bx35_inh} * y_{305} / V_{lam35}$,
 if $y_{265} < 0$ then $y_{265} = 0$ endif,
 $y_{266} = PS_{ap36_inh} * y_{226} * (V/div) / y_{36}$
 $(PS_{ax36_inh} + CL_{36_inh} + PS_{bp36_inh}) * f_{ent_inh} * y_{266} / Vent_{36} + PS_{bx36_inh} * y_{306} / V_{lam36}$,
 if $y_{266} < 0$ then $y_{266} = 0$ endif,
 $y_{267} = PS_{ap37_inh} * y_{227} * (V/div) / y_{37}$
 $(PS_{ax37_inh} + CL_{37_inh} + PS_{bp37_inh}) * f_{ent_inh} * y_{267} / Vent_{37} + PS_{bx37_inh} * y_{307} / V_{lam37}$,
 if $y_{267} < 0$ then $y_{267} = 0$ endif,
 $y_{268} = PS_{ap38_inh} * y_{228} * (V/div) / y_{38}$
 $(PS_{ax38_inh} + CL_{38_inh} + PS_{bp38_inh}) * f_{ent_inh} * y_{268} / Vent_{38} + PS_{bx38_inh} * y_{308} / V_{lam38}$,
 if $y_{268} < 0$ then $y_{268} = 0$ endif,
 $y_{269} = PS_{ap39_inh} * y_{229} * (V/div) / y_{39}$
 $(PS_{ax39_inh} + CL_{39_inh} + PS_{bp39_inh}) * f_{ent_inh} * y_{269} / Vent_{39} + PS_{bx39_inh} * y_{309} / V_{lam39}$,
 if $y_{269} < 0$ then $y_{269} = 0$ endif,
 $y_{270} = PS_{ap40_inh} * y_{230} * (V/div) / y_{40}$
 $(PS_{ax40_inh} + CL_{40_inh} + PS_{bp40_inh}) * f_{ent_inh} * y_{270} / Vent_{40} + PS_{bx40_inh} * y_{310} / V_{lam40}$,
 if $y_{270} < 0$ then $y_{270} = 0$ endif,

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$$y271' = \text{PSbp1_inh} * \text{fent_inh} * y231 / \text{Vent1} - (\text{Qlam1} / \text{fb_inh} + \text{PSbx1_inh}) * y271 / \text{Vlam1},$$

if $y271 < 0$ then $y271=0$ endif,

$$y272' = \text{PSbp2_inh} * \text{fent_inh} * y232 / \text{Vent2} - (\text{Qlam2} / \text{fb_inh} + \text{PSbx2_inh}) * y272 / \text{Vlam2},$$

if $y272 < 0$ then $y272=0$ endif,

$$y273' = \text{PSbp3_inh} * \text{fent_inh} * y233 / \text{Vent3} - (\text{Qlam3} / \text{fb_inh} + \text{PSbx3_inh}) * y273 / \text{Vlam3},$$

if $y273 < 0$ then $y273=0$ endif,

$$y274' = \text{PSbp4_inh} * \text{fent_inh} * y234 / \text{Vent4} - (\text{Qlam4} / \text{fb_inh} + \text{PSbx4_inh}) * y274 / \text{Vlam4},$$

if $y274 < 0$ then $y274=0$ endif,

$$y275' = \text{PSbp5_inh} * \text{fent_inh} * y235 / \text{Vent5} - (\text{Qlam5} / \text{fb_inh} + \text{PSbx5_inh}) * y275 / \text{Vlam5},$$

if $y275 < 0$ then $y275=0$ endif,

$$y276' = \text{PSbp6_inh} * \text{fent_inh} * y236 / \text{Vent6} - (\text{Qlam6} / \text{fb_inh} + \text{PSbx6_inh}) * y276 / \text{Vlam6},$$

if $y276 < 0$ then $y276=0$ endif,

$$y277' = \text{PSbp7_inh} * \text{fent_inh} * y237 / \text{Vent7} - (\text{Qlam7} / \text{fb_inh} + \text{PSbx7_inh}) * y277 / \text{Vlam7},$$

if $y277 < 0$ then $y277=0$ endif,

$$y278' = \text{PSbp8_inh} * \text{fent_inh} * y238 / \text{Vent8} - (\text{Qlam8} / \text{fb_inh} + \text{PSbx8_inh}) * y278 / \text{Vlam8},$$

if $y278 < 0$ then $y278=0$ endif,

$$y279' = \text{PSbp9_inh} * \text{fent_inh} * y239 / \text{Vent9} - (\text{Qlam9} / \text{fb_inh} + \text{PSbx9_inh}) * y279 / \text{Vlam9},$$

if $y279 < 0$ then $y279=0$ endif,

$$y280' = \text{PSbp10_inh} * \text{fent_inh} * y240 / \text{Vent10} - (\text{Qlam10} / \text{fb_inh} + \text{PSbx10_inh}) * y280 / \text{Vlam10},$$

if $y280 < 0$ then $y280=0$ endif,

$$y281' = \text{PSbp11_inh} * \text{fent_inh} * y241 / \text{Vent11} - (\text{Qlam11} / \text{fb_inh} + \text{PSbx11_inh}) * y281 / \text{Vlam11},$$

if $y281 < 0$ then $y281=0$ endif,

$$y282' = \text{PSbp12_inh} * \text{fent_inh} * y242 / \text{Vent12} - (\text{Qlam12} / \text{fb_inh} + \text{PSbx12_inh}) * y282 / \text{Vlam12},$$

if $y282 < 0$ then $y282=0$ endif,

$y_{283}' = PS_{bp13_inh} * f_{ent_inh} * y_{243} / Vent_{13} - (Q_{lam13} / fb_inh + PS_{bx13_inh}) * y_{283} / V_{lam13}$,
 if $y_{283} < 0$ then $y_{283} = 0$ endif,
 $y_{284}' = PS_{bp14_inh} * f_{ent_inh} * y_{244} / Vent_{14} - (Q_{lam14} / fb_inh + PS_{bx14_inh}) * y_{284} / V_{lam14}$,
 if $y_{284} < 0$ then $y_{284} = 0$ endif,
 $y_{285}' = PS_{bp15_inh} * f_{ent_inh} * y_{245} / Vent_{15} - (Q_{lam15} / fb_inh + PS_{bx15_inh}) * y_{285} / V_{lam15}$,
 if $y_{285} < 0$ then $y_{285} = 0$ endif,
 $y_{286}' = PS_{bp16_inh} * f_{ent_inh} * y_{246} / Vent_{16} - (Q_{lam16} / fb_inh + PS_{bx16_inh}) * y_{286} / V_{lam16}$,
 if $y_{286} < 0$ then $y_{286} = 0$ endif,
 $y_{287}' = PS_{bp17_inh} * f_{ent_inh} * y_{247} / Vent_{17} - (Q_{lam17} / fb_inh + PS_{bx17_inh}) * y_{287} / V_{lam17}$,
 if $y_{287} < 0$ then $y_{287} = 0$ endif,
 $y_{288}' = PS_{bp18_inh} * f_{ent_inh} * y_{248} / Vent_{18} - (Q_{lam18} / fb_inh + PS_{bx18_inh}) * y_{288} / V_{lam18}$,
 if $y_{288} < 0$ then $y_{288} = 0$ endif,
 $y_{289}' = PS_{bp19_inh} * f_{ent_inh} * y_{249} / Vent_{19} - (Q_{lam19} / fb_inh + PS_{bx19_inh}) * y_{289} / V_{lam19}$,
 if $y_{289} < 0$ then $y_{289} = 0$ endif,
 $y_{290}' = PS_{bp20_inh} * f_{ent_inh} * y_{250} / Vent_{20} - (Q_{lam20} / fb_inh + PS_{bx20_inh}) * y_{290} / V_{lam20}$,
 if $y_{290} < 0$ then $y_{290} = 0$ endif,
 $y_{291}' = PS_{bp21_inh} * f_{ent_inh} * y_{251} / Vent_{21} - (Q_{lam21} / fb_inh + PS_{bx21_inh}) * y_{291} / V_{lam21}$,
 if $y_{291} < 0$ then $y_{291} = 0$ endif,
 $y_{292}' = PS_{bp22_inh} * f_{ent_inh} * y_{252} / Vent_{22} - (Q_{lam22} / fb_inh + PS_{bx22_inh}) * y_{292} / V_{lam22}$,
 if $y_{292} < 0$ then $y_{292} = 0$ endif,
 $y_{293}' = PS_{bp23_inh} * f_{ent_inh} * y_{253} / Vent_{23} - (Q_{lam23} / fb_inh + PS_{bx23_inh}) * y_{293} / V_{lam23}$,
 if $y_{293} < 0$ then $y_{293} = 0$ endif,
 $y_{294}' = PS_{bp24_inh} * f_{ent_inh} * y_{254} / Vent_{24} - (Q_{lam24} / fb_inh + PS_{bx24_inh}) * y_{294} / V_{lam24}$,
 if $y_{294} < 0$ then $y_{294} = 0$ endif,
 $y_{295}' = PS_{bp25_inh} * f_{ent_inh} * y_{255} / Vent_{25} - (Q_{lam25} / fb_inh + PS_{bx25_inh}) * y_{295} / V_{lam25}$,

if $y_{295} < 0$ then $y_{295}=0$ endif,
 $y_{296}' = PS_{bp26_inh} * f_{ent_inh} * y_{256} / Vent_{26} - (Q_{lam26} / fb_{inh} + PS_{bx26_inh}) * y_{296} / V_{lam26}$,
 if $y_{296} < 0$ then $y_{296}=0$ endif,
 $y_{297}' = PS_{bp27_inh} * f_{ent_inh} * y_{257} / Vent_{27} - (Q_{lam27} / fb_{inh} + PS_{bx27_inh}) * y_{297} / V_{lam27}$,
 if $y_{297} < 0$ then $y_{297}=0$ endif,
 $y_{298}' = PS_{bp28_inh} * f_{ent_inh} * y_{258} / Vent_{28} - (Q_{lam28} / fb_{inh} + PS_{bx28_inh}) * y_{298} / V_{lam28}$,
 if $y_{298} < 0$ then $y_{298}=0$ endif,
 $y_{299}' = PS_{bp29_inh} * f_{ent_inh} * y_{259} / Vent_{29} - (Q_{lam29} / fb_{inh} + PS_{bx29_inh}) * y_{299} / V_{lam29}$,
 if $y_{299} < 0$ then $y_{299}=0$ endif,
 $y_{300}' = PS_{bp30_inh} * f_{ent_inh} * y_{260} / Vent_{30} - (Q_{lam30} / fb_{inh} + PS_{bx30_inh}) * y_{300} / V_{lam30}$,
 if $y_{300} < 0$ then $y_{300}=0$ endif,
 $y_{301}' = PS_{bp31_inh} * f_{ent_inh} * y_{261} / Vent_{31} - (Q_{lam31} / fb_{inh} + PS_{bx31_inh}) * y_{301} / V_{lam31}$,
 if $y_{301} < 0$ then $y_{301}=0$ endif,
 $y_{302}' = PS_{bp32_inh} * f_{ent_inh} * y_{262} / Vent_{32} - (Q_{lam32} / fb_{inh} + PS_{bx32_inh}) * y_{302} / V_{lam32}$,
 if $y_{302} < 0$ then $y_{302}=0$ endif,
 $y_{303}' = PS_{bp33_inh} * f_{ent_inh} * y_{263} / Vent_{33} - (Q_{lam33} / fb_{inh} + PS_{bx33_inh}) * y_{303} / V_{lam33}$,
 if $y_{303} < 0$ then $y_{303}=0$ endif,
 $y_{304}' = PS_{bp34_inh} * f_{ent_inh} * y_{264} / Vent_{34} - (Q_{lam34} / fb_{inh} + PS_{bx34_inh}) * y_{304} / V_{lam34}$,
 if $y_{304} < 0$ then $y_{304}=0$ endif,
 $y_{305}' = PS_{bp35_inh} * f_{ent_inh} * y_{265} / Vent_{35} - (Q_{lam35} / fb_{inh} + PS_{bx35_inh}) * y_{305} / V_{lam35}$,
 if $y_{305} < 0$ then $y_{305}=0$ endif,
 $y_{306}' = PS_{bp36_inh} * f_{ent_inh} * y_{266} / Vent_{36} - (Q_{lam36} / fb_{inh} + PS_{bx36_inh}) * y_{306} / V_{lam36}$,
 if $y_{306} < 0$ then $y_{306}=0$ endif,
 $y_{307}' = PS_{bp37_inh} * f_{ent_inh} * y_{267} / Vent_{37} - (Q_{lam37} / fb_{inh} + PS_{bx37_inh}) * y_{307} / V_{lam37}$,
 if $y_{307} < 0$ then $y_{307}=0$ endif,

$y_{308}' = PS_{bp38_inh} * fent_inh * y_{268} / Vent_{38} - (Q_{lam38} / fb_inh + PS_{bx38_inh}) * y_{308} / V_{lam38}$,

if $y_{308} < 0$ then $y_{308} = 0$ endif,

$y_{309}' = PS_{bp39_inh} * fent_inh * y_{269} / Vent_{39} - (Q_{lam39} / fb_inh + PS_{bx39_inh}) * y_{309} / V_{lam39}$,

if $y_{309} < 0$ then $y_{309} = 0$ endif,

$y_{310}' = PS_{bp40_inh} * fent_inh * y_{270} / Vent_{40} - (Q_{lam40} / fb_inh + PS_{bx40_inh}) * y_{310} / V_{lam40}$,

if $y_{310} < 0$ then $y_{310} = 0$ endif,

; Drug amount in the colon

$y_{311}' = ((9.0 y_{230} - y_{229}) / 8.0) Q - k_{rec} * y_{311}$,

; Drug amount in the feces

$y_{312}' = k_{rec} * y_{311} * V_c$,

; Drug concentration in the stomach

$y_{313}' = k_a * y_{320} * V_{es} / V_g - k_g * y_{313}$,

; % of dose in stomach (not used in this study)

$y_{314} = y_{313} V_g / dose_inh * 100$,

; % of dose in jejunum (not used in this study)

$y_{315} = (y_{191} + y_{192} + y_{193} + y_{194} + y_{195} + y_{196} + y_{197} + y_{198} + y_{199} + y_{200} + y_{201} + y_{202} + y_{203} + y_{204} + y_{205} + y_{206} + y_{207} + y_{208} + y_{209} + y_{210}) V / div / dose_inh * 100$,

; % of dose in ileum (not used in this study)

$y_{316} = (y_{211} + y_{212} + y_{213} + y_{214} + y_{215} + y_{216} + y_{217} + y_{218} + y_{219} + y_{220} + y_{221} + y_{222} + y_{223} + y_{224} + y_{225} + y_{226} + y_{227} + y_{228} + y_{229} + y_{230}) V / \text{div} / \text{dose_inh} * 100,$

; % of dose in colon(not used in this study)

$y_{317} = y_{311} V_c / \text{dose_inh} * 100,$

; % of dose in whole lumen (not used in this study)

$y_{318} = y_{315} + y_{316} + y_{317},$

; Drug amount in the gastrointestinal tract (not used in this study)

$y_{319} = y_{314} + y_{315} + y_{316} + y_{317},$

; Drug concentration in the esophagus

$y_{320}' = -k_a * y_{320},$

; not used in this study

$y_{321} = y_{320}$

; Drug amount in the enterocytes

$y_{322} = (y_{231} + y_{232} + y_{233} + y_{234} + y_{235} + y_{236} + y_{237} + y_{238} + y_{239} + y_{240} + y_{241} + y_{242} + y_{243} + y_{244} + y_{245} + y_{246} + y_{247} + y_{248} + y_{249} + y_{250} + y_{251} + y_{252} + y_{253} + y_{254} + y_{255} + y_{256} + y_{257} + y_{258} + y_{259} + y_{260} + y_{261} + y_{262} + y_{263} + y_{264} + y_{265} + y_{266} + y_{267} + y_{268} + y_{269} + y_{270}),$

; Drug amount in the lamina propria

$$y_{323} = (y_{231} + y_{232} + y_{233} + y_{234} + y_{235} + y_{236} + y_{237} + y_{238} + y_{239} + y_{240} + y_{241} + y_{242} + y_{243} + y_{244} + y_{245} + y_{246} + y_{247} + y_{248} + y_{249} + y_{250} + y_{251} + y_{252} + y_{253} + y_{254} + y_{255} + y_{256} + y_{257} + y_{258} + y_{259} + y_{260} + y_{261} + y_{262} + y_{263} + y_{264} + y_{265} + y_{266} + y_{267} + y_{268} + y_{269} + y_{270}),$$

; Drug accumulated amount in the portal vein

$$y_{324}' =$$

$$(y_{271}/V_{lam1} * Q_{lam1} + y_{272}/V_{lam2} * Q_{lam2} + y_{273}/V_{lam3} * Q_{lam3} + y_{274}/V_{lam4} * Q_{lam4} + y_{275}/V_{lam5} * Q_{lam5} + y_{276}/V_{lam6} * Q_{lam6} + y_{277}/V_{lam7} * Q_{lam7} + y_{278}/V_{lam8} * Q_{lam8} + y_{279}/V_{lam9} * Q_{lam9} + y_{280}/V_{lam10} * Q_{lam10} + y_{281}/V_{lam11} * Q_{lam11} + y_{282}/V_{lam12} * Q_{lam12} + y_{283}/V_{lam13} * Q_{lam13} + y_{284}/V_{lam14} * Q_{lam14} + y_{285}/V_{lam15} * Q_{lam15} + y_{286}/V_{lam16} * Q_{lam16} + y_{287}/V_{lam17} * Q_{lam17} + y_{288}/V_{lam18} * Q_{lam18} + y_{289}/V_{lam19} * Q_{lam19} + y_{290}/V_{lam20} * Q_{lam20} + y_{291}/V_{lam21} * Q_{lam21} + y_{292}/V_{lam22} * Q_{lam22} + y_{293}/V_{lam23} * Q_{lam23} + y_{294}/V_{lam24} * Q_{lam24} + y_{295}/V_{lam25} * Q_{lam25} + y_{296}/V_{lam26} * Q_{lam26} + y_{297}/V_{lam27} * Q_{lam27} + y_{298}/V_{lam28} * Q_{lam28} + y_{299}/V_{lam29} * Q_{lam29} + y_{300}/V_{lam30} * Q_{lam30} + y_{301}/V_{lam31} * Q_{lam31} + y_{302}/V_{lam32} * Q_{lam32} + y_{303}/V_{lam33} * Q_{lam33} + y_{304}/V_{lam34} * Q_{lam34} + y_{305}/V_{lam35} * Q_{lam35} + y_{306}/V_{lam36} * Q_{lam36} + y_{307}/V_{lam37} * Q_{lam37} + y_{308}/V_{lam38} * Q_{lam38} + y_{309}/V_{lam39} * Q_{lam39} + y_{310}/V_{lam40} * Q_{lam40})/fb_inh,$$

; F_A of an inhibitor

$$y_{325} = 1 - y_{311}/dose_inh,$$

; F_{AFG} of an inhibitor

$$y_{326} = y_{324}/dose_inh,$$

; F_G of an inhibitor

$$y_{327} = y_{326} / y_{325},$$

; Intestinal clearance amount

$$y_{328}' = \text{CL1_inh} * y_{231} / \text{Vent1} + \text{CL2_inh} * y_{232} / \text{Vent2} + \text{CL3_inh} * y_{233} / \text{Vent3} + \text{CL4_inh} * y_{234} / \text{Vent4} + \text{CL5_inh} * y_{235} / \text{Vent5} + \text{CL6_inh} * y_{236} / \text{Vent6} + \text{CL7_inh} * y_{237} / \text{Vent7} + \text{CL8_inh} * y_{238} / \text{Vent8} + \text{CL9_inh} * y_{239} / \text{Vent9} + \text{CL10_inh} * y_{240} / \text{Vent10} + \text{CL11_inh} * y_{241} / \text{Vent11} + \text{CL12_inh} * y_{242} / \text{Vent12} + \text{CL13_inh} * y_{243} / \text{Vent13} + \text{CL14_inh} * y_{244} / \text{Vent14} + \text{CL15_inh} * y_{245} / \text{Vent15} + \text{CL16_inh} * y_{246} / \text{Vent16} + \text{CL17_inh} * y_{247} / \text{Vent17} + \text{CL18_inh} * y_{248} / \text{Vent18} + \text{CL19_inh} * y_{249} / \text{Vent19} + \text{CL20_inh} * y_{250} / \text{Vent20} + \text{CL21_inh} * y_{251} / \text{Vent21} + \text{CL22_inh} * y_{252} / \text{Vent22} + \text{CL23_inh} * y_{253} / \text{Vent23} + \text{CL24_inh} * y_{254} / \text{Vent24} + \text{CL25_inh} * y_{255} / \text{Vent25} + \text{CL26_inh} * y_{256} / \text{Vent26} + \text{CL27_inh} * y_{257} / \text{Vent27} + \text{CL28_inh} * y_{258} / \text{Vent28} + \text{CL29_inh} * y_{259} / \text{Vent29} + \text{CL30_inh} * y_{260} / \text{Vent30} + \text{CL31_inh} * y_{261} / \text{Vent31} + \text{CL32_inh} * y_{262} / \text{Vent32} + \text{CL33_inh} * y_{263} / \text{Vent33} + \text{CL34_inh} * y_{264} / \text{Vent34} + \text{CL35_inh} * y_{265} / \text{Vent35} + \text{CL36_inh} * y_{266} / \text{Vent36} + \text{CL37_inh} * y_{267} / \text{Vent37} + \text{CL38_inh} * y_{268} / \text{Vent38} + \text{CL39_inh} * y_{269} / \text{Vent39} + \text{CL40_inh} * y_{270} / \text{Vent40},$$

; Drug amount in the portal vein

$$y_{329}'$$

$$= (y_{271} / \text{Vlam1} * \text{Qlam1} + y_{272} / \text{Vlam2} * \text{Qlam2} + y_{273} / \text{Vlam3} * \text{Qlam3} + y_{274} / \text{Vlam4} * \text{Qlam4} + y_{275} / \text{Vlam5} * \text{Qlam5} + y_{276} / \text{Vlam6} * \text{Qlam6} + y_{277} / \text{Vlam7} * \text{Qlam7} + y_{278} / \text{Vlam8} * \text{Qlam8} + y_{279} / \text{Vlam9} * \text{Qlam9} + y_{280} / \text{Vlam10} * \text{Qlam10} + y_{281} / \text{Vlam11} * \text{Qlam11} + y_{282} / \text{Vlam12} * \text{Qlam12} + y_{283} / \text{Vlam13} * \text{Qlam13} + y_{284} / \text{Vlam14} * \text{Qlam14} + y_{285} / \text{Vlam15} * \text{Qlam15} + y_{286} / \text{Vlam16} * \text{Qlam16} + y_{287} / \text{Vlam17} * \text{Qlam17} + y_{288} / \text{Vlam18} * \text{Qlam18} + y_{289} / \text{Vlam19} * \text{Qlam19} + y_{290} / \text{Vlam20} * \text{Qlam20} + y_{291} / \text{Vlam21} * \text{Qlam21} + y_{292} / \text{Vlam22} * \text{Qlam22} + y_{293} / \text{Vlam23} * \text{Qlam23} + y_{294} / \text{Vlam24} * \text{Qlam24} + y_{295} / \text{Vlam25} * \text{Qlam25} + y_{296} / \text{Vlam26} * \text{Qlam26} + y_{297} / \text{Vlam27} * \text{Qlam27} + y_{298} / \text{Vlam28} * \text{Qlam28} + y_{299} / \text{Vlam29} * \text{Qlam29} + y_{300} / \text{Vlam30} * \text{Qlam30} + y_{301} / \text{Vlam31} * \text{Qlam31} + y_{302} / \text{Vlam32} * \text{Qlam32} + y_{303} / \text{Vlam33} * \text{Qlam33} + y_{304} / \text{Vlam34} * \text{Qlam34} + y_{305} / \text{Vlam35} * \text{Qlam35} + y_{306} / \text{Vlam36} * \text{Qlam36} + y_{307} / \text{Vlam37} * \text{Qlam37} + y_{308} / \text{Vlam38} * \text{Qlam38} + y_{309} / \text{Vlam39} * \text{Qlam39} + y_{310} / \text{Vlam40} * \text{Qlam40})$$

$m32*Qlam32+y303/Vlam33*Qlam33+y304/Vlam34*Qlam34+y305/Vlam35*Qlam35+y306$
 $/Vlam36*Qlam36+y307/Vlam37*Qlam37+y308/Vlam38*Qlam38+y309/Vlam39*Qlam39+$
 $y310/Vlam40*Qlam40)/fb_inh-Qpv*y329/Vpv,$

; Drug concentration in the liver

$y330'=(Qpv*y329/Vpv-Qh*y330/Kp_liver_inh*Rb_inh-$
 $fb_inh*Rb_inh/Kp_liver_inh*CLint_h_inh*y330+Qha*y331)/Vliver,$

; Drug concentration in the blood

$y331'=(Qh*y330/Kp_liver_inh*Rb_inh-Qha*y331-$
 $k12_inh*y331*Vb+k21_inh*y332)/Vb_inh,$

; Drug concentration in the peripheral compartment 1

; The number of peripheral compartments can be increased as necessary.

$y332'=k12_inh*y331*Vb_inh-k21*y332,$

; Drug concentration in the blood (unit: ug/L)

$y333=y331*1000,$

; Whole drug concentration of a substrate in the enterocytes

$y334 =$

$(y101+y102+y103+y104+y105+y106+y107+y108+y109+y110+y111+y112+y113+y114+y1$
 $15+y116+y117+y118+y119+y120+y121+y122+y123+y124+y125+y126+y127+y128+y129+$
 $y130+y131+y132+y133+y134+y135+y136+y137+y138+y139+y140)/(Vent1+Vent2+Vent3$
 $+Vent4+Vent5+Vent6+Vent7+Vent8+Vent9+Vent10+Vent11+Vent12+Vent13+Vent14+Ve$

nt15+Vent16+Vent17+Vent18+Vent19+Vent20+Vent21+Vent22+Vent23+Vent24+Vent25+
Vent26+Vent27+Vent28+Vent29+Vent30+Vent31+Vent32+Vent33+Vent34+Vent35+Vent3
6+Vent37+Vent38+Vent39+Vent40)

; Drug concentration of a substrate in each compartment of the enterocytes

$$y335 = y101/Vent1,$$

$$y336 = y102/Vent2,$$

$$y337 = y103/Vent3,$$

$$y338 = y104/Vent4,$$

$$y339 = y105/Vent5,$$

$$y340 = y106/Vent6,$$

$$y341 = y107/Vent7,$$

$$y342 = y108/Vent8,$$

$$y343 = y109/Vent9,$$

$$y344 = y110/Vent10,$$

$$y345 = y111/Vent11,$$

$$y346 = y112/Vent12,$$

$$y347 = y113/Vent13,$$

$$y348 = y114/Vent14,$$

$$y349 = y115/Vent15,$$

$$y350 = y116/Vent16,$$

$$y351 = y117/Vent17,$$

$$y352 = y118/Vent18,$$

$$y353 = y119/Vent19,$$

$$y354 = y120/Vent20,$$

$$y355 = y121/Vent21,$$

$$y356 = y122/Vent22,$$

$$y357 = y123/Vent23,$$

$$y358 = y124/Vent24,$$

$$y359 = y125/Vent25,$$

$$y360 = y126/Vent26,$$

$$y361 = y127/Vent27,$$

$$y362 = y128/Vent28,$$

$$y363 = y129/Vent29,$$

$$y364 = y130/Vent30,$$

$$y365 = y131/Vent31,$$

$$y366 = y132/Vent32,$$

$$y367 = y133/Vent33,$$

$$y368 = y134/Vent34,$$

$$y369 = y135/Vent35,$$

$$y370 = y136/Vent36,$$

$$y371 = y137/Vent37,$$

$$y372 = y138/Vent38,$$

$$y373 = y139/Vent39,$$

$$y374 = y140/Vent40,$$

; Drug accumulation of a substrate in each compartment of the portal vein

$$y375' = y141/Vlam1 * Qlam1 / fb / dose,$$

$$y376' = y142/Vlam2 * Qlam2 / fb / dose,$$

$$y377' = y143/Vlam3 * Qlam3 / fb / dose,$$

y378'=y144/Vlam4*Qlam4/fb/dose,
y379'=y145/Vlam5*Qlam5/fb/dose,
y380'=y146/Vlam6*Qlam6/fb/dose,
y381'=y147/Vlam7*Qlam7/fb/dose,
y382'=y148/Vlam8*Qlam8/fb/dose,
y383'=y149/Vlam9*Qlam9/fb/dose,
y384'=y150/Vlam10*Qlam10/fb/dose,
y385'=y151/Vlam11*Qlam11/fb/dose,
y386'=y152/Vlam12*Qlam12/fb/dose,
y387'=y153/Vlam13*Qlam13/fb/dose,
y388'=y154/Vlam14*Qlam14/fb/dose,
y389'=y155/Vlam15*Qlam15/fb/dose,
y390'=y156/Vlam16*Qlam16/fb/dose,
y391'=y157/Vlam17*Qlam17/fb/dose,
y392'=y158/Vlam18*Qlam18/fb/dose,
y393'=y159/Vlam19*Qlam19/fb/dose,
y394'=y160/Vlam20*Qlam20/fb/dose,
y395'=y161/Vlam21*Qlam21/fb/dose,
y396'=y162/Vlam22*Qlam22/fb/dose,
y397'=y163/Vlam23*Qlam23/fb/dose,
y398'=y164/Vlam24*Qlam24/fb/dose,
y399'=y165/Vlam25*Qlam25/fb/dose,
y400'=y166/Vlam26*Qlam26/fb/dose,
y401'=y167/Vlam27*Qlam27/fb/dose,
y402'=y168/Vlam28*Qlam28/fb/dose,

$y_{403}' = y_{169} / V_{lam29} * Q_{lam29} / fb / dose,$
 $y_{404}' = y_{170} / V_{lam30} * Q_{lam30} / fb / dose,$
 $y_{405}' = y_{171} / V_{lam31} * Q_{lam31} / fb / dose,$
 $y_{406}' = y_{172} / V_{lam32} * Q_{lam32} / fb / dose,$
 $y_{407}' = y_{173} / V_{lam33} * Q_{lam33} / fb / dose,$
 $y_{408}' = y_{174} / V_{lam34} * Q_{lam34} / fb / dose,$
 $y_{409}' = y_{175} / V_{lam35} * Q_{lam35} / fb / dose,$
 $y_{410}' = y_{176} / V_{lam36} * Q_{lam36} / fb / dose,$
 $y_{411}' = y_{177} / V_{lam37} * Q_{lam37} / fb / dose,$
 $y_{412}' = y_{178} / V_{lam38} * Q_{lam38} / fb / dose,$
 $y_{413}' = y_{179} / V_{lam39} * Q_{lam39} / fb / dose,$
 $y_{414}' = y_{180} / V_{lam40} * Q_{lam40} / fb / dose,$

; ***** Preparative Calculation *****div = 40,

; 40 is number of segments

; in this model, dispersion is defined by volume not by length

$$b = Q \text{ div} / V,$$

$$k_{wn} = kw / \text{div},$$

; section 1

$$D_{sp_1} = A * \exp(-B * x_1) + 0.005,$$

$$a_1 = D_{sp_1} Q \text{ div} \text{ div} / V,$$

$$c1_1 = -a_1 / 12 - b / 12,$$

$$c2_1 = a_1^{4/3} + b^{2/3},$$

$$c3_1 = -a_1^{5/2}, ; -ke,$$

$$c4_1 = a_1^{4/3} - b^{2/3},$$

$$c5_1 = -a_1/12 + b/12,$$

$$c3a_1 = -c1_1 + c3_1 + c4_1 + c5_1,$$

$$c4a_1 = c4_1 + c5_1,$$

$$c2a_1 = c1_1 + c2_1,$$

$$kw_1 = kw,$$

$$sw_1 = sw,$$

; section 2

$$Dsp_2 = A * \exp(-B * x_2) + 0.005,$$

$$a_2 = Dsp_2 Q \text{ div div} / V,$$

$$c1_2 = -a_2/12 - b/12,$$

$$c2_2 = a_2^{4/3} + b^{2/3},$$

$$c3_2 = -a_2^{5/2}, ; -ke,$$

$$c4_2 = a_2^{4/3} - b^{2/3},$$

$$c5_2 = -a_2/12 + b/12,$$

$$c3a_2 = -c1_2 + c3_2 + c4_2 + c5_2,$$

$$c4a_2 = c4_2 + c5_2,$$

$$c2a_2 = c1_2 + c2_2,$$

$$c3_2_kw = c3_2 - kw,$$

$$sw_2 = sw,$$

; section 3

$$Dsp_3 = A * \exp(-B * x_3) + 0.005,$$

$$a_3 = Dsp_3 Q \text{ div div} / V,$$

$$c1_3 = -a_3/12 - b/12,$$

$$c2_3 = a_3^{4/3} + b^{2/3},$$

$$c3_3 = -a_3^{5/2}, ; - ke,$$

$$c4_3 = a_3^{4/3} - b^{2/3},$$

$$c5_3 = -a_3/12 + b/12,$$

$$c3_3_{kw} = c3_3 - kw,$$

$$sw_3 = sw,$$

; section 4

$$Dsp_4 = A * \exp(-B * x_4) + 0.005,$$

$$a_4 = Dsp_4 Q \text{ div div} / V,$$

$$c1_4 = -a_4/12 - b/12,$$

$$c2_4 = a_4^{4/3} + b^{2/3},$$

$$c3_4 = -a_4^{5/2}, ; - ke,$$

$$c4_4 = a_4^{4/3} - b^{2/3},$$

$$c5_4 = -a_4/12 + b/12,$$

$$c3_4_{kw} = c3_4 - kw,$$

$$sw_4 = sw,$$

; section 5

$$Dsp_5 = A * \exp(-B * x_5) + 0.005,$$

$$a_5 = Dsp_5 Q \text{ div div} / V,$$

$$c1_5 = -a_5/12 - b/12,$$

$$c2_5 = a_5^{4/3} + b^{2/3},$$

$$c3_5 = -a_5^{5/2}, ; - ke,$$

$$c4_5 = a_5^{4/3} - b^{2/3},$$

$$c5_5 = -a_5/12 + b/12,$$

$$c3_5_{kw} = c3_5 - kw,$$

$$sw_5 = sw,$$

; section 6

$$Dsp_6 = A * \exp(-B * x_6) + 0.005,$$

$$a_6 = Dsp_6 Q \text{ div div} / V,$$

$$c1_6 = -a_6/12 - b/12,$$

$$c2_6 = a_6^{4/3} + b^{2/3},$$

$$c3_6 = -a_6^{5/2}, ; - ke,$$

$$c4_6 = a_6^{4/3} - b^{2/3},$$

$$c5_6 = -a_6/12 + b/12,$$

$$c3_6_{kw} = c3_6 - kw,$$

$$sw_6 = sw,$$

; section 7

$$Dsp_7 = A * \exp(-B * x_7) + 0.005,$$

$$a_7 = Dsp_7 Q \text{ div div} / V,$$

$$c1_7 = -a_7/12 - b/12,$$

$$c2_7 = a_7^{4/3} + b^{2/3},$$

$$c3_7 = -a_7^{5/2}, ; - ke,$$

$$c4_7 = a_7^{4/3} - b^{2/3},$$

$$c5_7 = -a_7/12 + b/12,$$

$$c3_7_{kw} = c3_7 - kw,$$

$$sw_7 = sw,$$

; section 8

$$Dsp_8 = A * \exp(-B * x_8) + 0.005,$$

$$a_8 = Dsp_8 Q \operatorname{div} \operatorname{div} / V,$$

$$c1_8 = -a_8/12 - b/12,$$

$$c2_8 = a_8^{4/3} + b^{2/3},$$

$$c3_8 = -a_8^{5/2}, ; - ke,$$

$$c4_8 = a_8^{4/3} - b^{2/3},$$

$$c5_8 = -a_8/12 + b/12,$$

$$c3_8_{kw} = c3_8 - kw,$$

$$sw_8 = sw,$$

; section 9

$$Dsp_9 = A * \exp(-B * x_9) + 0.005,$$

$$a_9 = Dsp_9 Q \operatorname{div} \operatorname{div} / V,$$

$$c1_9 = -a_9/12 - b/12,$$

$$c2_9 = a_9^{4/3} + b^{2/3},$$

$$c3_9 = -a_9^{5/2}, ; - ke,$$

$$c4_9 = a_9^{4/3} - b^{2/3},$$

$$c5_9 = -a_9/12 + b/12,$$

$$c3_9_kw = c3_9 - kw,$$

$$sw_9 = sw,$$

; section 10

$$Dsp_10 = A * \exp(-B * x_10) + 0.005,$$

$$a_10 = Dsp_10 Q \text{ div div} / V,$$

$$c1_10 = -a_10/12 - b/12,$$

$$c2_10 = a_10^{4/3} + b^{2/3},$$

$$c3_10 = -a_10^{5/2}, ; - ke,$$

$$c4_10 = a_10^{4/3} - b^{2/3},$$

$$c5_10 = -a_10/12 + b/12,$$

$$c3_10_kw = c3_10 - kw,$$

$$sw_10 = sw,$$

; section 11

$$Dsp_11 = A * \exp(-B * x_11) + 0.005,$$

$$a_11 = Dsp_11 Q \text{ div div} / V,$$

$$c1_11 = -a_11/12 - b/12,$$

$$c2_{11} = a_{11}^{4/3} + b^{2/3},$$

$$c3_{11} = -a_{11}^{5/2}, ; -ke,$$

$$c4_{11} = a_{11}^{4/3} - b^{2/3},$$

$$c5_{11} = -a_{11}/12 + b/12,$$

$$c3_{11_kw} = c3_{11} - kw,$$

$$sw_{11} = sw,$$

; section 12

$$Dsp_{12} = A * \exp(-B * x_{12}) + 0.005,$$

$$a_{12} = Dsp_{12} Q \text{ div div} / V,$$

$$c1_{12} = -a_{12}/12 - b/12,$$

$$c2_{12} = a_{12}^{4/3} + b^{2/3},$$

$$c3_{12} = -a_{12}^{5/2}, ; -ke,$$

$$c4_{12} = a_{12}^{4/3} - b^{2/3},$$

$$c5_{12} = -a_{12}/12 + b/12,$$

$$c3_{12_kw} = c3_{12} - kw,$$

$$sw_{12} = sw,$$

; section 13

$$Dsp_{13} = A * \exp(-B * x_{13}) + 0.005,$$

$$a_{13} = Dsp_{13} Q \text{ div div} / V,$$

$$c1_{13} = -a_{13}/12 - b/12,$$

$$c2_{13} = a_{13}^{4/3} + b^{2/3},$$

$$c3_{13} = -a_{13}^{5/2}, ; - ke,$$

$$c4_{13} = a_{13}^{4/3} - b^{2/3},$$

$$c5_{13} = -a_{13}/12 + b/12,$$

$$c3_{13_kw} = c3_{13} - kw,$$

$$sw_{13} = sw,$$

; section 14

$$Dsp_{14} = A * \exp(-B * x_{14}) + 0.005,$$

$$a_{14} = Dsp_{14} Q \text{ div div} / V,$$

$$c1_{14} = -a_{14}/12 - b/12,$$

$$c2_{14} = a_{14}^{4/3} + b^{2/3},$$

$$c3_{14} = -a_{14}^{5/2}, ; - ke,$$

$$c4_{14} = a_{14}^{4/3} - b^{2/3},$$

$$c5_{14} = -a_{14}/12 + b/12,$$

$$c3_{14_kw} = c3_{14} - kw,$$

$$sw_{14} = sw,$$

; section 15

$$Dsp_{15} = A * \exp(-B * x_{15}) + 0.005,$$

$$a_{15} = Dsp_{15} Q \text{ div div} / V,$$

$$c1_{15} = -a_{15}/12 - b/12,$$

$$c2_{15} = a_{15}^{4/3} + b^{2/3},$$

$$c3_{15} = -a_{15}^{5/2}, ; - ke,$$

$$c4_{15} = a_{15}^{4/3} - b^{2/3},$$

$$c5_{15} = -a_{15}/12 + b/12,$$

$$c3_{15_kw} = c3_{15} - kw,$$

$$sw_{15} = sw,$$

; section 16

$$Dsp_{16} = A * \exp(-B * x_{16}) + 0.005,$$

$$a_{16} = Dsp_{16} Q \text{ div div} / V,$$

$$c1_{16} = -a_{16}/12 - b/12,$$

$$c2_{16} = a_{16}^{4/3} + b^{2/3},$$

$$c3_{16} = -a_{16}^{5/2}, ; - ke,$$

$$c4_{16} = a_{16}^{4/3} - b^{2/3},$$

$$c5_{16} = -a_{16}/12 + b/12,$$

$$c3_{16_kw} = c3_{16} - kw,$$

$$sw_{16} = sw,$$

; section 17

$$Dsp_{17} = A * \exp(-B * x_{17}) + 0.005,$$

$$a_{17} = Dsp_{17} Q \text{ div div} / V,$$

$$c1_{17} = -a_{17}/12 - b/12,$$

$$c2_{17} = a_{17}^{4/3} + b^{2/3},$$

$$c3_{17} = -a_{17}^{5/2}, ; - ke,$$

$$c4_{17} = a_{17}^{4/3} - b^{2/3},$$

$$c5_{17} = -a_{17}/12 + b/12,$$

$$c3_{17_kw} = c3_{17} - kw,$$

$$sw_{17} = sw,$$

; section 18

$$Dsp_{18} = A * \exp(-B * x_{18}) + 0.005,$$

$$a_{18} = Dsp_{18} Q \text{ div div} / V,$$

$$c1_{18} = -a_{18}/12 - b/12,$$

$$c2_{18} = a_{18}^{4/3} + b^{2/3},$$

$$c3_{18} = -a_{18}^{5/2}, ; - ke,$$

$$c4_{18} = a_{18}^{4/3} - b^{2/3},$$

$$c5_{18} = -a_{18}/12 + b/12,$$

$$c3_{18_kw} = c3_{18} - kw,$$

$$sw_{18} = sw,$$

; section 19

$$Dsp_{19} = A * \exp(-B * x_{19}) + 0.005,$$

$$a_{19} = Dsp_{19} Q \text{ div div} / V,$$

$$c1_{19} = -a_{19}/12 - b/12,$$

$$c2_{19} = a_{19}^{4/3} + b^{2/3},$$

$$c3_{19} = -a_{19}^{5/2}, ; - ke,$$

$$c4_{19} = a_{19}^{4/3} - b^{2/3},$$

$$c5_{19} = -a_{19}/12 + b/12,$$

$$c3_{19_kw} = c3_{19-kw},$$

$$sw_{19}=sw,$$

; section 20

$$Dsp_{20}=A*\exp(-B*x_{20})+0.005,$$

$$a_{20} = Dsp_{20} Q \text{ div div} / V,$$

$$c1_{20}= -a_{20}/12 - b/12,$$

$$c2_{20}= a_{20}^{4/3} + b^{2/3},$$

$$c3_{20}= -a_{20}^{5/2}, ; - ke,$$

$$c4_{20}= a_{20}^{4/3} - b^{2/3},$$

$$c5_{20}= -a_{20}/12 + b/12,$$

$$c3_{20_kw} = c3_{20-kw},$$

$$sw_{20}=sw,$$

; section 21

$$Dsp_{21}= A*\exp(-B*x_{21})+0.005,$$

$$a_{21} = Dsp_{21} Q \text{ div div} / V,$$

$$c1_{21}= -a_{21}/12 - b/12,$$

$$c2_{21}= a_{21}^{4/3} + b^{2/3},$$

$$c3_{21}= -a_{21}^{5/2}, ; - ke,$$

$$c4_{21}= a_{21}^{4/3} - b^{2/3},$$

$$c5_{21}= -a_{21}/12 + b/12,$$

$$c3_{21_kw} = c3_{21-kw},$$

$$sw_{21}=sw,$$

; section 22

$$Dsp_{22}= A*\exp(-B*x_{22})+0.005,$$

$$a_{22} = Dsp_{22} Q \text{ div div} / V,$$

$$c1_{22}= -a_{22}/12 - b/12,$$

$$c2_{22}= a_{22}^{4/3} + b^{2/3},$$

$$c3_{22}= -a_{22}^{5/2}, ; - ke,$$

$$c4_{22}= a_{22}^{4/3} - b^{2/3},$$

$$c5_{22}= -a_{22}/12 + b/12,$$

$$c3_{22_kw} = c3_{22}-kw,$$

$$sw_{22}=sw,$$

; section 23

$$Dsp_{23}= A*\exp(-B*x_{23})+0.005,$$

$$a_{23} = Dsp_{23} Q \text{ div div} / V,$$

$$c1_{23}= -a_{23}/12 - b/12,$$

$$c2_{23}= a_{23}^{4/3} + b^{2/3},$$

$$c3_{23}= -a_{23}^{5/2}, ; - ke,$$

$$c4_{23}= a_{23}^{4/3} - b^{2/3},$$

$$c5_{23}= -a_{23}/12 + b/12,$$

$$c3_{23_kw} = c3_{23}-kw,$$

$$sw_{23}=sw,$$

; section 24

$$Dsp_{24} = A * \exp(-B * x_{24}) + 0.005,$$

$$a_{24} = Dsp_{24} Q \text{ div div} / V,$$

$$c1_{24} = -a_{24}/12 - b/12,$$

$$c2_{24} = a_{24}^{4/3} + b^{2/3},$$

$$c3_{24} = -a_{24}^{5/2}, ; - ke,$$

$$c4_{24} = a_{24}^{4/3} - b^{2/3},$$

$$c5_{24} = -a_{24}/12 + b/12,$$

$$c3_{24_kw} = c3_{24} - kw,$$

$$sw_{24} = sw,$$

; section 25

$$Dsp_{25} = A * \exp(-B * x_{25}) + 0.005,$$

$$a_{25} = Dsp_{25} Q \text{ div div} / V,$$

$$c1_{25} = -a_{25}/12 - b/12,$$

$$c2_{25} = a_{25}^{4/3} + b^{2/3},$$

$$c3_{25} = -a_{25}^{5/2}, ; - ke,$$

$$c4_{25} = a_{25}^{4/3} - b^{2/3},$$

$$c5_{25} = -a_{25}/12 + b/12,$$

$$c3_{25_kw} = c3_{25} - kw,$$

$$sw_{25} = sw,$$

; section 26

$$Dsp_{26} = A * \exp(-B * x_{26}) + 0.005,$$

$$a_{26} = Dsp_{26} Q \text{ div div} / V,$$

$$c1_{26} = -a_{26}/12 - b/12,$$

$$c2_{26} = a_{26}^{4/3} + b^{2/3},$$

$$c3_{26} = -a_{26}^{5/2}, ; - ke,$$

$$c4_{26} = a_{26}^{4/3} - b^{2/3},$$

$$c5_{26} = -a_{26}/12 + b/12,$$

$$c3_{26_kw} = c3_{26} - kw,$$

$$sw_{26} = sw,$$

; section 27

$$Dsp_{27} = A * \exp(-B * x_{27}) + 0.005,$$

$$a_{27} = Dsp_{27} Q \text{ div div} / V,$$

$$c1_{27} = -a_{27}/12 - b/12,$$

$$c2_{27} = a_{27}^{4/3} + b^{2/3},$$

$$c3_{27} = -a_{27}^{5/2}, ; - ke,$$

$$c4_{27} = a_{27}^{4/3} - b^{2/3},$$

$$c5_{27} = -a_{27}/12 + b/12,$$

$$c3_{27_kw} = c3_{27} - kw,$$

$$sw_{27} = sw,$$

; section 28

$$Dsp_{28} = A * \exp(-B * x_{28}) + 0.005,$$

$$a_{28} = Dsp_{28} Q \text{ div div} / V,$$

$$c1_{28} = -a_{28}/12 - b/12,$$

$$c2_{28} = a_{28}^{4/3} + b^{2/3},$$

$$c3_{28} = -a_{28}^{5/2}, ; - ke,$$

$$c4_{28} = a_{28}^{4/3} - b^{2/3},$$

$$c5_{28} = -a_{28}/12 + b/12,$$

$$c3_{28_kw} = c3_{28} - kw,$$

$$sw_{28} = sw,$$

; section 29

$$Dsp_{29} = A * \exp(-B * x_{29}) + 0.005,$$

$$a_{29} = Dsp_{29} Q \text{ div div} / V,$$

$$c1_{29} = -a_{29}/12 - b/12,$$

$$c2_{29} = a_{29}^{4/3} + b^{2/3},$$

$$c3_{29} = -a_{29}^{5/2}, ; - ke,$$

$$c4_{29} = a_{29}^{4/3} - b^{2/3},$$

$$c5_{29} = -a_{29}/12 + b/12,$$

$$c3_{29_kw} = c3_{29} - kw,$$

$$sw_{29} = sw,$$

; section 30

$$Dsp_{30} = A * \exp(-B * x_{30}) + 0.005,$$

$$a_{30} = \text{Dsp}_{30} Q \text{ div div} / V,$$

$$c1_{30} = -a_{30}/12 - b/12,$$

$$c2_{30} = a_{30}^{4/3} + b^{2/3},$$

$$c3_{30} = -a_{30}^{5/2}, ; - ke,$$

$$c4_{30} = a_{30}^{4/3} - b^{2/3},$$

$$c5_{30} = -a_{30}/12 + b/12,$$

$$c3_{30_kw} = c3_{30} - kw,$$

$$sw_{30} = sw,$$

; section 31

$$\text{Dsp}_{31} = A * \exp(-B * x_{31}) + 0.005,$$

$$a_{31} = \text{Dsp}_{31} Q \text{ div div} / V,$$

$$c1_{31} = -a_{31}/12 - b/12,$$

$$c2_{31} = a_{31}^{4/3} + b^{2/3},$$

$$c3_{31} = -a_{31}^{5/2}, ; - ke,$$

$$c4_{31} = a_{31}^{4/3} - b^{2/3},$$

$$c5_{31} = -a_{31}/12 + b/12,$$

$$c3_{31_kw} = c3_{31} - kw,$$

$$sw_{31} = sw,$$

; section 32

$$\text{Dsp}_{32} = A * \exp(-B * x_{32}) + 0.005,$$

$$a_{32} = \text{Dsp}_{32} Q \text{ div div} / V,$$

$$c1_{32} = -a_{32}/12 - b/12,$$

$$c2_{32} = a_{32} \frac{4}{3} + b \frac{2}{3},$$

$$c3_{32} = -a_{32} \frac{5}{2}, ; - ke,$$

$$c4_{32} = a_{32} \frac{4}{3} - b \frac{2}{3},$$

$$c5_{32} = -a_{32}/12 + b/12,$$

$$c3_{32_kw} = c3_{32} - kw,$$

$$sw_{32} = sw,$$

; section 33

$$Dsp_{33} = A * \exp(-B * x_{33}) + 0.005,$$

$$a_{33} = Dsp_{33} Q \text{ div div} / V,$$

$$c1_{33} = -a_{33}/12 - b/12,$$

$$c2_{33} = a_{33} \frac{4}{3} + b \frac{2}{3},$$

$$c3_{33} = -a_{33} \frac{5}{2}, ; - ke,$$

$$c4_{33} = a_{33} \frac{4}{3} - b \frac{2}{3},$$

$$c5_{33} = -a_{33}/12 + b/12,$$

$$c3_{33_kw} = c3_{33} - kw,$$

$$sw_{33} = sw,$$

; section 34

$$Dsp_{34} = A * \exp(-B * x_{34}) + 0.005,$$

$$a_{34} = Dsp_{34} Q \text{ div div} / V,$$

$$c1_{34} = -a_{34}/12 - b/12,$$

$$c2_{34} = a_{34}^{4/3} + b^{2/3},$$

$$c3_{34} = -a_{34}^{5/2}, ; - ke,$$

$$c4_{34} = a_{34}^{4/3} - b^{2/3},$$

$$c5_{34} = -a_{34}/12 + b/12,$$

$$c3_{34_kw} = c3_{34} - kw,$$

$$sw_{34} = sw,$$

; section 35

$$Dsp_{35} = A * \exp(-B * x_{35}) + 0.005,$$

$$a_{35} = Dsp_{35} Q \text{ div div} / V,$$

$$c1_{35} = -a_{35}/12 - b/12,$$

$$c2_{35} = a_{35}^{4/3} + b^{2/3},$$

$$c3_{35} = -a_{35}^{5/2}, ; - ke,$$

$$c4_{35} = a_{35}^{4/3} - b^{2/3},$$

$$c5_{35} = -a_{35}/12 + b/12,$$

$$c3_{35_kw} = c3_{35} - kw,$$

$$sw_{35} = sw,$$

; section 36

$$Dsp_{36} = A * \exp(-B * x_{36}) + 0.005,$$

$$a_{36} = Dsp_{36} Q \text{ div div} / V,$$

$$c1_{36} = -a_{36}/12 - b/12,$$

$$c2_{36} = a_{36}^{4/3} + b^{2/3},$$

$$c3_{36} = -a_{36}^{5/2}, ; -ke,$$

$$c4_{36} = a_{36}^{4/3} - b^{2/3},$$

$$c5_{36} = -a_{36}/12 + b/12,$$

$$c3_{36_kw} = c3_{36} - kw,$$

$$sw_{36} = sw,$$

; section 37

$$Dsp_{37} = A * \exp(-B * x_{37}) + 0.005,$$

$$a_{37} = Dsp_{37} Q \text{ div div} / V,$$

$$c1_{37} = -a_{37}/12 - b/12,$$

$$c2_{37} = a_{37}^{4/3} + b^{2/3},$$

$$c3_{37} = -a_{37}^{5/2}, ; -ke,$$

$$c4_{37} = a_{37}^{4/3} - b^{2/3},$$

$$c5_{37} = -a_{37}/12 + b/12,$$

$$c3_{37_kw} = c3_{37} - kw,$$

$$sw_{37} = sw,$$

; section 38

$$Dsp_{38} = A * \exp(-B * x_{38}) + 0.005,$$

$$a_{38} = Dsp_{38} Q \text{ div div} / V,$$

$$c1_{38} = -a_{38}/12 - b/12,$$

$$c2_{38} = a_{38}^{4/3} + b^{2/3},$$

$$c3_38 = -a_38^{5/2}, ; - ke,$$

$$c4_38 = a_38^{4/3} - b^{2/3},$$

$$c5_38 = -a_38/12 + b/12,$$

$$c3_38_kw = c3_38 - kw,$$

$$sw_38 = sw,$$

; section 39

$$Dsp_39 = A * \exp(-B * x_39) + 0.005,$$

$$a_39 = Dsp_39 Q \text{ div div} / V,$$

$$c1_39 = -a_39/12 - b/12,$$

$$c2_39 = a_39^{4/3} + b^{2/3},$$

$$c3_39 = -a_39^{5/2}, ; - ke,$$

$$c4_39 = a_39^{4/3} - b^{2/3},$$

$$c5_39 = -a_39/12 + b/12,$$

$$c4a_39 = c4_39 + c5_39,$$

$$c2b_39 = c2_39 + c5_39,$$

$$c3b_39 = c3_39 + c4_39,$$

$$c3_39_kw = c3_39 - kw,$$

$$sw_39 = sw,$$

; section 40

$$Dsp_40 = A * \exp(-B * x_40) + 0.005,$$

$$a_40 = Dsp_40 Q \text{ div div} / V,$$

$$c1_40 = -a_40/12 - b/12,$$

$$c2_40 = a_40^{4/3} + b^{2/3},$$

$$c3_40 = -a_40^{5/2}, \text{ ; - ke,}$$

$$c4_40 = a_40^{4/3} - b^{2/3},$$

$$c5_40 = -a_40/12 + b/12,$$

$$c4a_40 = c4_40 + c5_40,$$

$$c2b_40 = c2_40 + c5_40,$$

$$c3b_40 = c3_40 + c4_40,$$

$$kw_40 = kw,$$

$$sw_40 = sw,$$

; Translation from Permeability in Caco-2 cells to in vivo permeability (Substrate)

$$P_Caco2 = (1+ME_Caco2)/ME_Caco2 Papp_Caco2,$$

$$P_invivo = P_Caco2 \text{ psf_passive,}$$

; Translation from Permeability in Caco-2 cells to in vivo permeability (Perpetrator)

$$P_Caco2_inh = (1+ME_Caco2)/ME_Caco2 Papp_Caco2_inh,$$

$$P_invivo_inh = P_Caco2_inh \text{ psf_passive,}$$

; ratio of blood flow in lamina propria at each compartment

$$Qlam1 = Qlam * Sapi_ratio1,$$

$$Qlam2 = Qlam * Sapi_ratio2,$$

$$Qlam3 = Qlam * Sapi_ratio3,$$

$$Qlam4 = Qlam * Sapi_ratio4,$$

$$Qlam5 = Qlam * Sapi_ratio5,$$

$Q_{lam6} = Q_{lam} * Sapi_ratio6,$
 $Q_{lam7} = Q_{lam} * Sapi_ratio7,$
 $Q_{lam8} = Q_{lam} * Sapi_ratio8,$
 $Q_{lam9} = Q_{lam} * Sapi_ratio9,$
 $Q_{lam10} = Q_{lam} * Sapi_ratio10,$
 $Q_{lam11} = Q_{lam} * Sapi_ratio11,$
 $Q_{lam12} = Q_{lam} * Sapi_ratio12,$
 $Q_{lam13} = Q_{lam} * Sapi_ratio13,$
 $Q_{lam14} = Q_{lam} * Sapi_ratio14,$
 $Q_{lam15} = Q_{lam} * Sapi_ratio15,$
 $Q_{lam16} = Q_{lam} * Sapi_ratio16,$
 $Q_{lam17} = Q_{lam} * Sapi_ratio17,$
 $Q_{lam18} = Q_{lam} * Sapi_ratio18,$
 $Q_{lam19} = Q_{lam} * Sapi_ratio19,$
 $Q_{lam20} = Q_{lam} * Sapi_ratio20,$
 $Q_{lam21} = Q_{lam} * Sapi_ratio21,$
 $Q_{lam22} = Q_{lam} * Sapi_ratio22,$
 $Q_{lam23} = Q_{lam} * Sapi_ratio23,$
 $Q_{lam24} = Q_{lam} * Sapi_ratio24,$
 $Q_{lam25} = Q_{lam} * Sapi_ratio25,$
 $Q_{lam26} = Q_{lam} * Sapi_ratio26,$
 $Q_{lam27} = Q_{lam} * Sapi_ratio27,$
 $Q_{lam28} = Q_{lam} * Sapi_ratio28,$
 $Q_{lam29} = Q_{lam} * Sapi_ratio29,$
 $Q_{lam30} = Q_{lam} * Sapi_ratio30,$

$$Qlam31 = Qlam * Sapi_ratio31,$$

$$Qlam32 = Qlam * Sapi_ratio32,$$

$$Qlam33 = Qlam * Sapi_ratio33,$$

$$Qlam34 = Qlam * Sapi_ratio34,$$

$$Qlam35 = Qlam * Sapi_ratio35,$$

$$Qlam36 = Qlam * Sapi_ratio36,$$

$$Qlam37 = Qlam * Sapi_ratio37,$$

$$Qlam38 = Qlam * Sapi_ratio38,$$

$$Qlam39 = Qlam * Sapi_ratio39,$$

$$Qlam40 = Qlam * Sapi_ratio40,$$

; Volume of caecum and colon

$$Vcae_col = Vcae + Vc,$$

; Relative Expression of P-gp in the small intestine

$$Arel_Pgp1 = (1 + x_1/Lsi)^2 * Tot_Pgp / (3 * Lsi)^{x_1/2},$$

$$Arel_Pgp2 = (1 + x_1/Lsi + 1 + x_2/Lsi)^2 * Tot_Pgp / (3 * Lsi)^{(x_2 - x_1)/2},$$

$$Arel_Pgp3 = (1 + x_2/Lsi + 1 + x_3/Lsi)^2 * Tot_Pgp / (3 * Lsi)^{(x_3 - x_2)/2},$$

$$Arel_Pgp4 = (1 + x_3/Lsi + 1 + x_4/Lsi)^2 * Tot_Pgp / (3 * Lsi)^{(x_4 - x_3)/2},$$

$$Arel_Pgp5 = (1 + x_4/Lsi + 1 + x_5/Lsi)^2 * Tot_Pgp / (3 * Lsi)^{(x_5 - x_4)/2},$$

$$Arel_Pgp6 = (1 + x_5/Lsi + 1 + x_6/Lsi)^2 * Tot_Pgp / (3 * Lsi)^{(x_6 - x_5)/2},$$

$$Arel_Pgp7 = (1 + x_6/Lsi + 1 + x_7/Lsi)^2 * Tot_Pgp / (3 * Lsi)^{(x_7 - x_6)/2},$$

$$Arel_Pgp8 = (1 + x_7/Lsi + 1 + x_8/Lsi)^2 * Tot_Pgp / (3 * Lsi)^{(x_8 - x_7)/2},$$

$$Arel_Pgp9 = (1 + x_8/Lsi + 1 + x_9/Lsi)^2 * Tot_Pgp / (3 * Lsi)^{(x_9 - x_8)/2},$$

$$Arel_Pgp10 = (1 + x_9/Lsi + 1 + x_{10}/Lsi)^2 * Tot_Pgp / (3 * Lsi)^{(x_{10} - x_9)/2},$$

$$\text{Arel_Pgp11}=(1+x_{10}/\text{Lsi}+1+x_{11}/\text{Lsi})^2*\text{Tot_Pgp}/(3*\text{Lsi})*(x_{11}-x_{10})/2,$$

$$\text{Arel_Pgp12}=(1+x_{11}/\text{Lsi}+1+x_{12}/\text{Lsi})^2*\text{Tot_Pgp}/(3*\text{Lsi})*(x_{12}-x_{11})/2,$$

$$\text{Arel_Pgp13}=(1+x_{12}/\text{Lsi}+1+x_{13}/\text{Lsi})^2*\text{Tot_Pgp}/(3*\text{Lsi})*(x_{13}-x_{12})/2,$$

$$\text{Arel_Pgp14}=(1+x_{13}/\text{Lsi}+1+x_{14}/\text{Lsi})^2*\text{Tot_Pgp}/(3*\text{Lsi})*(x_{14}-x_{13})/2,$$

$$\text{Arel_Pgp15}=(1+x_{14}/\text{Lsi}+1+x_{15}/\text{Lsi})^2*\text{Tot_Pgp}/(3*\text{Lsi})*(x_{15}-x_{14})/2,$$

$$\text{Arel_Pgp16}=(1+x_{15}/\text{Lsi}+1+x_{16}/\text{Lsi})^2*\text{Tot_Pgp}/(3*\text{Lsi})*(x_{16}-x_{15})/2,$$

$$\text{Arel_Pgp17}=(1+x_{16}/\text{Lsi}+1+x_{17}/\text{Lsi})^2*\text{Tot_Pgp}/(3*\text{Lsi})*(x_{17}-x_{16})/2,$$

$$\text{Arel_Pgp18}=(1+x_{17}/\text{Lsi}+1+x_{18}/\text{Lsi})^2*\text{Tot_Pgp}/(3*\text{Lsi})*(x_{18}-x_{17})/2,$$

$$\text{Arel_Pgp19}=(1+x_{18}/\text{Lsi}+1+x_{19}/\text{Lsi})^2*\text{Tot_Pgp}/(3*\text{Lsi})*(x_{19}-x_{18})/2,$$

$$\text{Arel_Pgp20}=(1+x_{19}/\text{Lsi}+1+x_{20}/\text{Lsi})^2*\text{Tot_Pgp}/(3*\text{Lsi})*(x_{20}-x_{19})/2,$$

$$\text{Arel_Pgp21}=(1+x_{20}/\text{Lsi}+1+x_{21}/\text{Lsi})^2*\text{Tot_Pgp}/(3*\text{Lsi})*(x_{21}-x_{20})/2,$$

$$\text{Arel_Pgp22}=(1+x_{21}/\text{Lsi}+1+x_{22}/\text{Lsi})^2*\text{Tot_Pgp}/(3*\text{Lsi})*(x_{22}-x_{21})/2,$$

$$\text{Arel_Pgp23}=(1+x_{22}/\text{Lsi}+1+x_{23}/\text{Lsi})^2*\text{Tot_Pgp}/(3*\text{Lsi})*(x_{23}-x_{22})/2,$$

$$\text{Arel_Pgp24}=(1+x_{23}/\text{Lsi}+1+x_{24}/\text{Lsi})^2*\text{Tot_Pgp}/(3*\text{Lsi})*(x_{24}-x_{23})/2,$$

$$\text{Arel_Pgp25}=(1+x_{24}/\text{Lsi}+1+x_{25}/\text{Lsi})^2*\text{Tot_Pgp}/(3*\text{Lsi})*(x_{25}-x_{24})/2,$$

$$\text{Arel_Pgp26}=(1+x_{25}/\text{Lsi}+1+x_{26}/\text{Lsi})^2*\text{Tot_Pgp}/(3*\text{Lsi})*(x_{26}-x_{25})/2,$$

$$\text{Arel_Pgp27}=(1+x_{26}/\text{Lsi}+1+x_{27}/\text{Lsi})^2*\text{Tot_Pgp}/(3*\text{Lsi})*(x_{27}-x_{26})/2,$$

$$\text{Arel_Pgp28}=(1+x_{27}/\text{Lsi}+1+x_{28}/\text{Lsi})^2*\text{Tot_Pgp}/(3*\text{Lsi})*(x_{28}-x_{27})/2,$$

$$\text{Arel_Pgp29}=(1+x_{28}/\text{Lsi}+1+x_{29}/\text{Lsi})^2*\text{Tot_Pgp}/(3*\text{Lsi})*(x_{29}-x_{28})/2,$$

$$\text{Arel_Pgp30}=(1+x_{29}/\text{Lsi}+1+x_{30}/\text{Lsi})^2*\text{Tot_Pgp}/(3*\text{Lsi})*(x_{30}-x_{29})/2,$$

$$\text{Arel_Pgp31}=(1+x_{30}/\text{Lsi}+1+x_{31}/\text{Lsi})^2*\text{Tot_Pgp}/(3*\text{Lsi})*(x_{31}-x_{30})/2,$$

$$\text{Arel_Pgp32}=(1+x_{31}/\text{Lsi}+1+x_{32}/\text{Lsi})^2*\text{Tot_Pgp}/(3*\text{Lsi})*(x_{32}-x_{31})/2,$$

$$\text{Arel_Pgp33}=(1+x_{32}/\text{Lsi}+1+x_{33}/\text{Lsi})^2*\text{Tot_Pgp}/(3*\text{Lsi})*(x_{33}-x_{32})/2,$$

$$\text{Arel_Pgp34}=(1+x_{33}/\text{Lsi}+1+x_{34}/\text{Lsi})^2*\text{Tot_Pgp}/(3*\text{Lsi})*(x_{34}-x_{33})/2,$$

$$\text{Arel_Pgp35}=(1+x_{34}/\text{Lsi}+1+x_{35}/\text{Lsi})^2*\text{Tot_Pgp}/(3*\text{Lsi})*(x_{35}-x_{34})/2,$$

$$\text{Arel_Pgp36}=(1+x_{35}/\text{Lsi}+1+x_{36}/\text{Lsi})^2*\text{Tot_Pgp}/(3*\text{Lsi})*(x_{36}-x_{35})/2,$$

$$\text{Arel_Pgp37}=(1+x_{36}/\text{Lsi}+1+x_{37}/\text{Lsi})^2*\text{Tot_Pgp}/(3*\text{Lsi})*(x_{37}-x_{36})/2,$$

$$\text{Arel_Pgp38}=(1+x_{37}/\text{Lsi}+1+x_{38}/\text{Lsi})^2*\text{Tot_Pgp}/(3*\text{Lsi})*(x_{38}-x_{37})/2,$$

$$\text{Arel_Pgp39}=(1+x_{38}/\text{Lsi}+1+x_{39}/\text{Lsi})^2*\text{Tot_Pgp}/(3*\text{Lsi})*(x_{39}-x_{38})/2,$$

$$\text{Arel_Pgp40}=(1+x_{39}/\text{Lsi}+1+x_{40}/\text{Lsi})^2*\text{Tot_Pgp}/(3*\text{Lsi})*(x_{40}-x_{39})/2,$$

Supplementary Table

Supplemental Table S1 Optimized parameters for intestinal water movement in ATOM

Parameter	Value	Unit
k_{es}	114.41	/h
$k_{water,sto}$	0	/h
$Se_{water,sto}$	88.63	mL/h
$k_{water,abs}$	881.26	/h
$Se_{water,abs}$	1500.00	mL/h

k_{es} : transit rate of drug (or water) from esophagus to stomach, $k_{water,sto}$: water absorption rate in stomach, $Se_{water,sto}$: water secretion clearance in stomach, $k_{water,abs}$: water absorption rate in lumen, $Se_{water,abs}$: water secretion clearance in lumen

Supplemental Table S2 Optimized parameters for transit rate from stomach to intestine, dispersion constants and intestinal flow rates using ^{99m}Tc -DTPA distribution in the lumen in ATOM

Subject and fasted/fe d	k_{sto} (h^{-1})	D_z (h^{-1})			M_t (h^{-1})		
		A	B	C	D	t_{lag}	E
Subject A fasted	4.27	816.59	0.082	11.34	0 ^a	-	1 ^a
Subject B fasted	5.23	584.19	0.044	15.00	0.92	1.05	1.01
Subject A fed	1.29	524.22	0.028	16.90	0.98	2.35	3.43
Subject B fed	0.89	201.76	0.031	12.50	0.91	2.12	1.82

These parameters were obtained by fitting analysis using ^{99m}Tc -DTPA distribution in the lumen reported by Haruta et al. .

a: Constant flow rate ($D=0$ and $E=1$) was adopted because AIC values were similar with the simulated results by ATOM using time-dependent flow rate.

k_{sto} : transit rate of drug or water from stomach to intestine, D_z : location-dependent dispersion number, M_t : time-dependent intestinal flow rate

Supplemental Table S3 Reported and optimized transit times in CAT using ^{99m}Tc -DTPA distribution in the lumen in both fasted and fed state.

Parameters	Value				Unit	
	Reported	Optimized				
		Subject A fasted	Subject B fasted	Subject A fed		Subject B fed
k_{sto}	4.00	4.17	3.45	1.11	0.77	/h
$k_{t,1}$	3.85	3.03	1.33	2.94	62.50	/h
$k_{t,2}$	1.08	3.03	208.33	357.14	2.33	/h
$k_{t,3}$	1.35	3.03	2.86	31.25	14.08	/h
$k_{t,4}$	1.72	0.81	1.64	9.09	0.65	/h
$k_{t,5}$	2.38	0.81	13.16	2.94	0.58	/h
$k_{t,6}$	3.45	0.81	0.68	0.20	58.82	/h

Each transit rate was calculated using the equation, Transit rate = 1/ Transit time. Reported transit times were referred from the report by Heikkinen et al. Optimized transit times were obtained by fitting analysis using observed distribution of ^{99m}Tc -DTPA in the lumen by Haruta et al.

k_{sto} : transit rate of drug or water from stomach to intestine, $k_{t,n}$: transit rate of drug or water from nth compartment in the lumen

Supplemental Table S4 Pharmacokinetic parameters of compounds

Parameter	Value	Unit	Reference and comment
midazolam			
$P_{app,Caco-2}$	0.117	cm/h	2
pKa	14 (acid), 4.57 (base)	-	ADMET Predictor® ver. 9.5
f_b	0.056	-	2
f_{ent}	0.056	-	Assumed to be equal with f_b
$V_{max,CYP3A}$	0.44	$\mu\text{g} / \text{h pmol}$ CYP3A	2
$K_m,CYP3A,u$	1.08	$\mu\text{g}/\text{mL}$	2
$K_{p,liver}$	6.96	-	3
R_B	0.55	-	4
CL_{int}	587336	mL/h	5 Optimized using plasma concentration after iv dosing
CL_R	0	mL/h	Assumed to be 0
$V_{central}$	99888	mL	5 Optimized using plasma concentration after iv dosing
k_{12}	0.288	/h	5 Optimized using plasma concentration after iv dosing
k_{21}	0.0042	/h	5 Optimized using plasma concentration after iv dosing

k_{12}^*	0.288	/h	Assumed to be same with k_{12}
k_{21}^*	0.0042	/h	Assumed to be same with k_{21}
Digoxin			
$P_{app,Caco-2}$	0.00396	cm/h	6
pKa	14(acid), 1(base)	-	ADMET Predictor® ver. 9.5
f_p	0.75	-	Digoxin Elixir, Printed Labeling
f_b	0.697	-	Calculated as $f_b=f_p/R_B$
f_{ent}	0.697	-	Assumed to be equal with f_b
$V_{max,P-gp}$	1.0×10^7	$\mu\text{g}/\text{h pmol}$	7
		P-gp	Optimized to the range of reported F_A values
$K_{m,Pgp,u}$	57	$\mu\text{g}/\text{mL}$	8
$K_{p,liver}$	1.35	-	GastroPlus® ver. 9.7
R_B	1.08	-	ADMET Predictor® ver. 9.0
CL_{int}^a	4793	mL/h	9
$CL_{R,Pgp}$	4080	mL/h	10
			Assumed from the CL_R change in P-gp inhibitor administration
$CL_{R,nonPgp}$	7560	mL/h	10
			Assumed from the CL_R change in P-gp inhibitor administration
$V_{central}$	11800	mL	10

k_{12}	2	/h	10	Optimized using plasma concentration of digoxin in iv administration
k_{21}	0.029	/h	10	Optimized using plasma concentration of digoxin in iv administration
k_{13}	2	/h	10	Optimized using plasma concentration of digoxin in iv administration
k_{31}	0.432	/h	10	Optimized using plasma concentration of digoxin in iv administration
k_{12}^*	2	/h		Assumed to be same with k_{12}
k_{21}^*	0.029	/h		Assumed to be same with k_{21}
k_{13}^*	2	/h		Assumed to be same with k_{13}
k_{31}^*	0.432	/h		Assumed to be same with k_{31}
itraconazole				
$P_{app,Caco-2}$	0.0245	cm/h	12	
pKa	14(acid), 4.57(base)	-		ADMET Predictor® ver. 9.5
f_b	0.0034	-		Calculated as $f_b=f_p/R_B$
f_p	0.002	-	13	

f_{ent}	0.0034	-	Assumed to be equal with f_b
$V_{max,CYP3A}$	0.0114	$\mu\text{g}/\text{h pmol}$ CYP3A	13
$K_{m,CYP3A,u}$	0.0313	$\mu\text{g}/\text{mL}$	13
$K_{p,liver}$	6.67	-	14
R_B	0.58	-	14
CL_{int}	14700000	mL/h	14
CL_R	0	mL/h	Assumed to be 0
$V_{central}$	59200	mL	14
$K_{i,CYP3A}$	0.212	$\mu\text{g}/\text{mL}$	35
clarithromycin			
$P_{app,Caco-2}$	0.0138	cm/h	15
pK_a	13.1(acid), 8.2(base)	-	16
f_b	0.32	-	16
f_{ent}	0.32	-	Assumed to be equal with f_b
$V_{max,CYP3A}$	0.013	$\mu\text{g}/\text{h pmol}$ CYP3A	24
$K_{m,CYP3A,u}$	36.43	$\mu\text{g}/\text{mL}$	17
LogP	2.3	-	18
R_B	0.74	-	16
CL_{int}	68504	mL/h	11
Optimized using plasma concentration of clarithromycin after po administration			

CL_R	6000	mL/h	19
V_{central}	25193	mL	20
			Optimized using plasma concentration of clarithromycin after iv administration
$K_{i,CYP3A}$	4.52	$\mu\text{g/mL}$	17
$K_{i,Pgp}$	324.61	$\mu\text{g/mL}$	32
k_{12}	8.91	/h	11
			Optimized using plasma concentration of clarithromycin after po administration
k_{21}	2.51	/h	11
			Optimized using plasma concentration of clarithromycin after po administration

a: The value was calculated using the number of hepatocytes (1.2×10^8 cells/g liver) and the weight of the liver (25.7 g liver/kg) (Watari et al., 2019)

Supplemental Table S5 Physiological parameters used in ATOM and CAT

Parameter	Value	Unit	Reference
Q_{pro}	18000	mL/h	2
Q_{pv}	37170	mL/h	3
Q_h	107100	mL/h	3
Q_{ha}	69930	mL/h	Calculated as $Q_{ha} = Q_h - Q_{pv}$
V_{es}	78.5	mL	Assumed a column with 1 cm radius and 25 cm length
V_{sto}	48.92	mL	GastroPlus® ver. 9.7
V_{pv}	70	mL	3
V_{liver}	1687	mL	3
V_{cae}	50.49	mL	GastroPlus® ver. 9.7
V_{col}	53.55	mL	GastroPlus® ver. 9.7
V_{si}	105	mL	31

Q_{pro} : blood flow of the blood capillaries in lamina propria, Q_{pv} : blood flow in the portal vein, Q_h : blood flow in the liver, Q_{ha} : arterial blood flow in the liver, V_{sto} : volume in the stomach, V_{pv} : volume in the portal vein, V_{liver} : volume in the liver, V_{cae} : volume in the caecum, V_{col} : volume in the colon, V_{si} : volume in the small intestine

Supplemental Table S6 Dataset for FG prediction about CYP3A or P-gp/CYP3A substrates and predicted or reported FG values

Compound	Dose	K _{m,u}		V _{max}		P _{app,caco-2}	f _b	pK _a ^a		F _G		
		CYP3A	P-gp	CYP3A	P-gp			acid	base	ATOM	TLM	Reported
	nmol	μg/mL	μg/mL	μg /h	μg /h	cm/h						
				pmol	pmol P-							
				CYP3A	gp							
alfentanil	7220	9.51	-	0.542	0	0.105	0.137	-	6.72	0.76	0.72	0.60
alprazolam	1290	81.9	-	0.074	0	0.0918	0.341	-	3.01	0.99	0.99	0.99
buspirone	4150	3.08	-	0.401	0	0.0914	0.062	-	7.16	0.56	0.51	0.22
cisapride	16100	1.49	-	0.245	0	0.108	0.020	11.2	7.30	0.63	0.56	0.55
cyclosporin	474000	1.68	0.0682	0.040	1.66×10 ⁶	0.0286	0.014	-	-	0.99	0.99	0.35

felodipine	26000	2.04	-	2.86	0	0.0151	0.068	10.95	0.51	0.02	0.02	0.53
lovastatin	49400	3.16	-	9.23	0	0.0522	0.030	-	-	0.04	0.04	0.09
midazolam	9200	1.08	-	0.440	0	0.117	0.056	-	4.57	0.39	0.36	0.48
nifedipine	28900	3.81	-	0.502	0	0.0846	0.066	11.06	1.28	0.63	0.60	0.74
nisoldipine	12900	0.815	-	3.75	0	0.072	0.003	11.2	0.68	0.03	0.03	0.11
rifabutin	177000	9.23	-	0.286	0	0.0342	0.483	6.92	8.12	0.94	0.85	0.21
saquinavir	1490000	0.201	0.579	0.731	1.66×10 ⁶	0.0497	0.038	10.83	6.40	0.94	0.92	0.18
sildenafil	52600	7.13	-	0.480	0	0.0922	0.063	9.38	7.60	0.78	0.77	0.54
simvastatin	95500	1.42	-	5.95	0	0.0245	0.025	-	-	0.02	0.02	0.19
trazodone	202000	116	-	1.64	0	0.0871	0.070	-	7.15	0.93	0.90	0.83
triazolam	729	29.2	-	0.090	0	0.101	0.161	-	2.85	0.98	0.98	0.45

zolpidem	16300	43.0	-	0.057	0	0.115	0.105	-	4.99	0.99	0.99	0.81
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Dataset of each compound, predicted (TLM) and reported F_G values were referred from the previous report by Ando et al.

a: Obtained from ADMET Predictor® version 9.5 (Simulations Plus Inc.)

Supplemental Table S7 Predictive performance of F_G values using ATOM and TLM compared with reported F_G values

Parameters	ATOM	TLM
Within ±0.3 (%)	65	71
AFE	1.06	1.10
RMSE	0.373	0.357

AFE: average fold error, RMSE: root mean square error

AFE and RMSE was calculated using the following equations. Parameter N represents the number of drugs.

$$\text{AFE} = 10^{\frac{\sum \log(\text{reported}/\text{predicted})}{N}}, \quad \text{RMSE} = \sqrt{\frac{\sum[(\text{predicted}-\text{reported})^2]}{N}}$$

Supplemental Table S8 Summary of AUCR ratio and F_G or F_A changes of digoxin and midazolam during DIs

midazolam^a

Perpetrator	AUCR ratio (predicted AUCR / reported AUCR)	F_G changes ($F_{G,p}/F_{G,control}$)
50 mg itraconazole	1.19	2.15
200 mg itraconazole	0.63	2.50
400 mg itraconazole	0.58	2.58

digoxin^b

Perpetrator	AUCR ratio (predicted AUCR / reported AUCR)	F_A changes ($F_{A,p}/F_{A,control}$)
250 mg clarithromycin	1.64	1.25

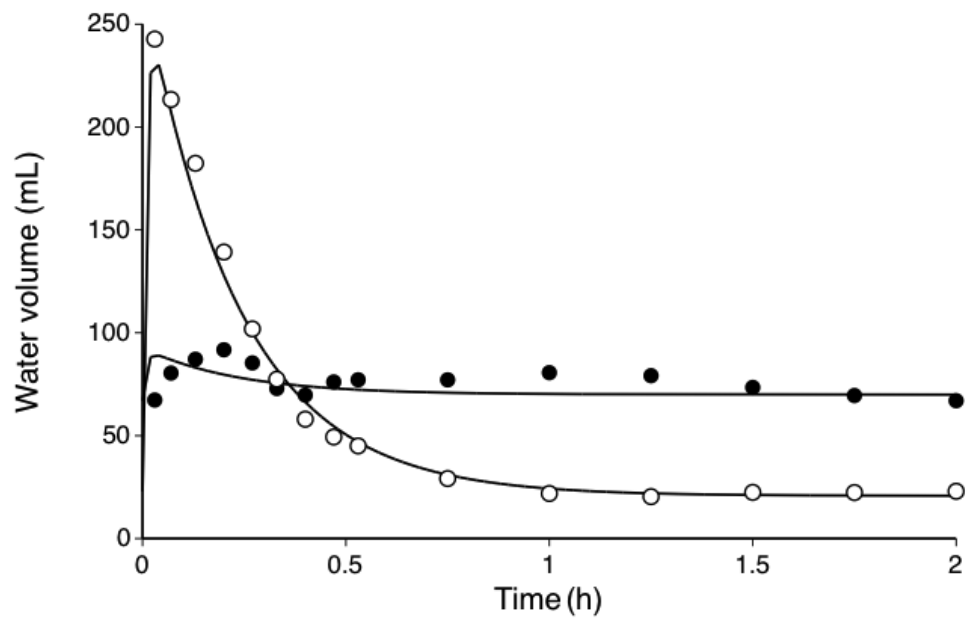
AUCR: AUC ratio, $F_{A,p}$: predicted F_A value of the substrate with the perpetrator, $F_{A,control}$: predicted F_A value of the substrate in the control, $F_{G,p}$: predicted F_G value of the substrate with the perpetrator, $F_{G,control}$: predicted F_G value of the substrate in the control

a: AUC_{inf} was used according to the report with the observed values by Templeton et al. (2010).

b: AUC_{0-24} was used according to the report with the observed values by Rengelshausen et al. (2003).

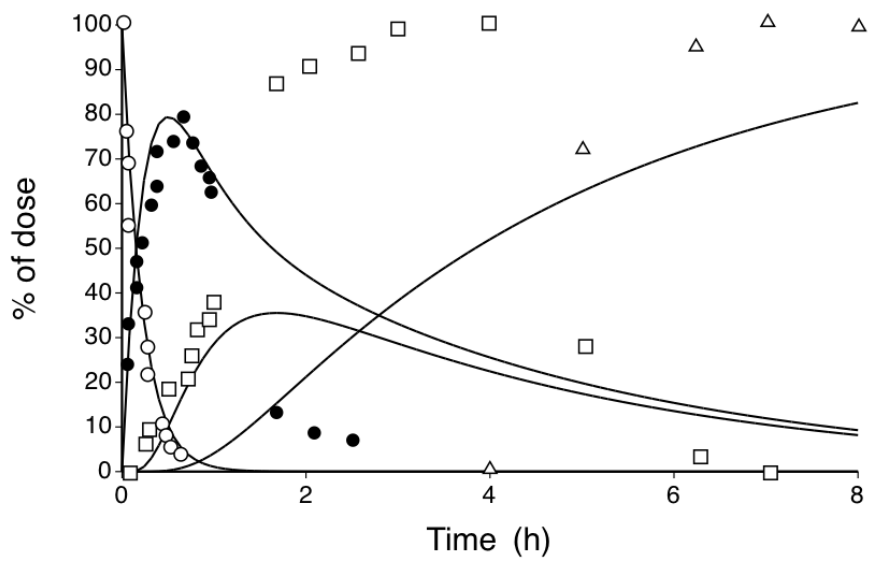
Supplementary Figures

Supplemental Fig. 1

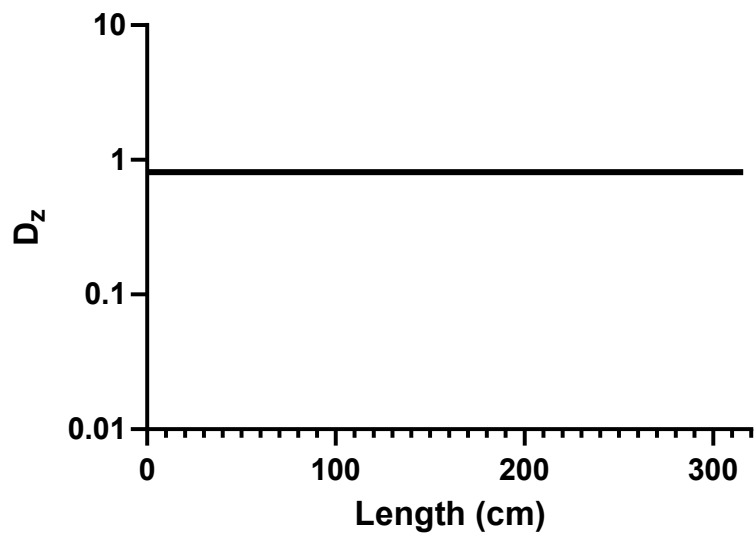


Supplemental Fig. 2

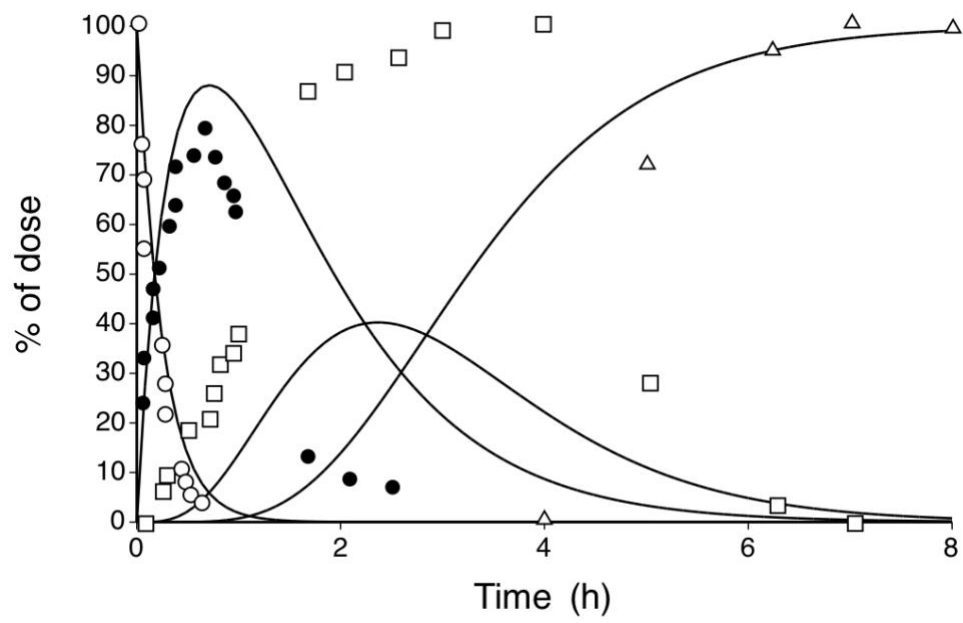
(A)



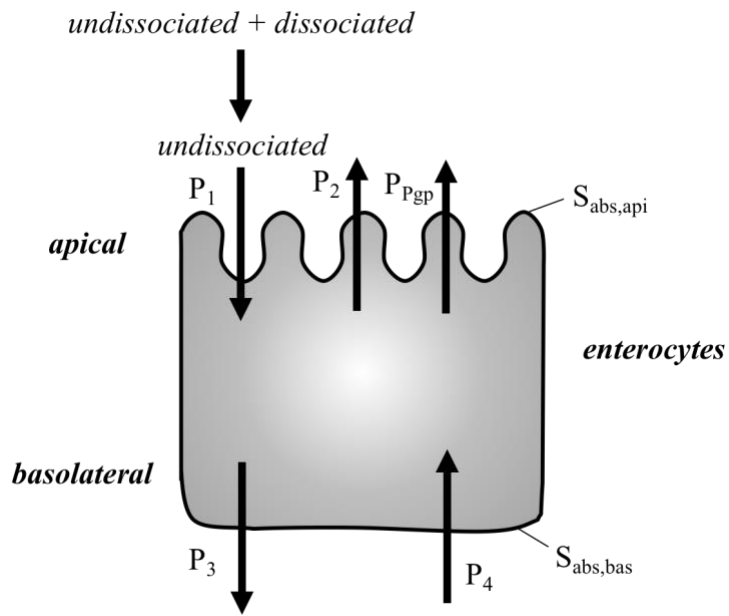
(B)



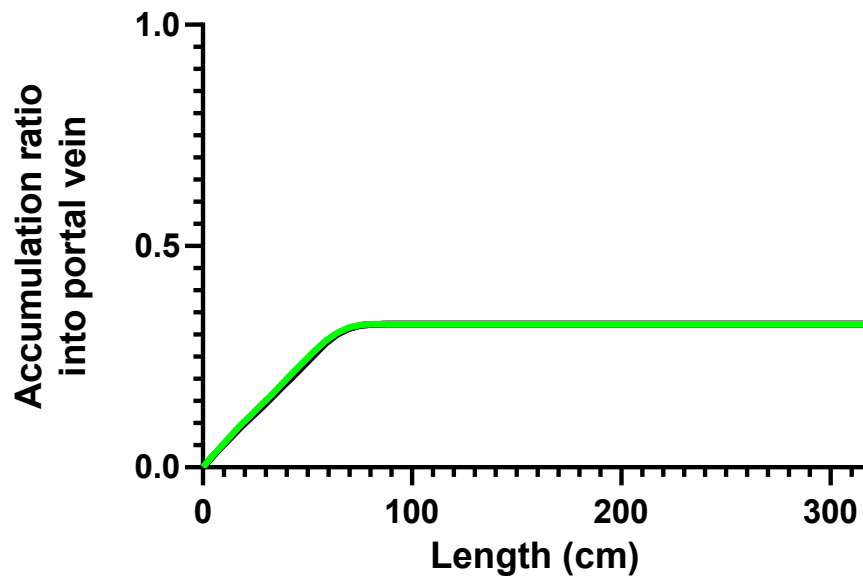
Supplemental Fig. 3



Supplemental Fig. 4

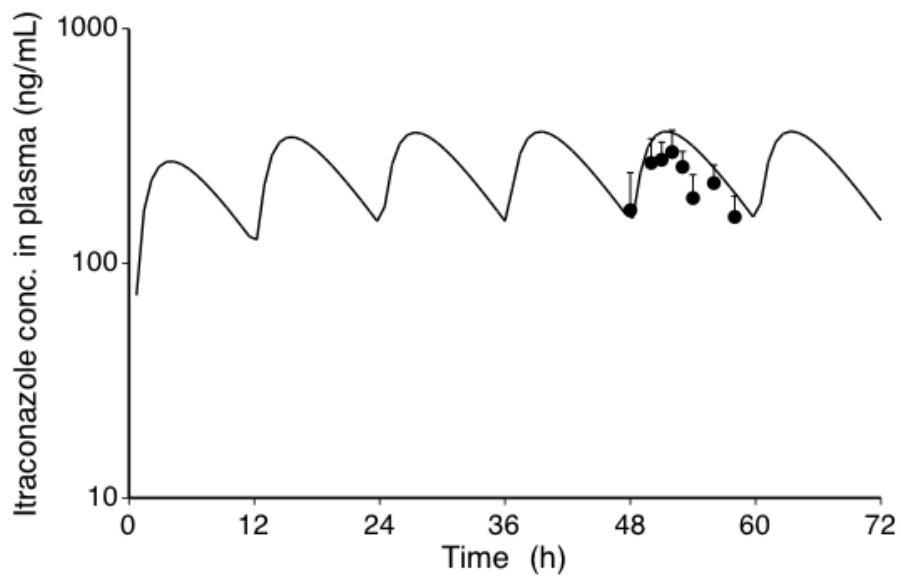


Supplemental Fig. 5



Supplemental Fig. 6

(A)



(B)

