Commentary: Theoretical Predictions of Flow Effects on Intestinal and Systemic Availability in Physiologically Based Pharmacokinetic Intestine Models: The Traditional Model, Segregated Flow Model, and QGut Model

K. Sandy Pang and Edwin C. Y. Chow

Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, Ontario, Canada

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ABSTRACT:
Physiologically based pharmacokinetic (PBPK) models for the intestine, comprising of different flow rates perfusing the enterocyte region, were revisited for appraisal of flow effects on the intestinal availability (FI) and, in turn, the systemic availability (Fsys) and intestinal versus liver contribution to the first-pass effect during oral drug absorption. The traditional model (TM), segregated flow model (SFM), and effective flow (QGut) model stipulate that 1.0, −0.05 to 0.3, and ≤0.484 × of the total intestinal flow, respectively, reach the enterocyte region that houses metabolically active and transporter-enriched enterocytes. The fractional flow rate to the enterocyte region (fQ), when examined under varying experimental conditions, was found to range from 0.024 to 0.2 for the SFM and 0.065 to 0.43 for the QGut model. Appraisal of these flow intestinal models, when used in combination with whole-body PBPK models, showed the ranking as SFM < QGut model < TM in the description of Fp, and the same ranking existed for the contribution of the intestine to first-pass removal. However, the ranking for the predicted contribution of hepatic metabolism, when present, to first-pass removal was the opposite: SFM > QGut model > TM. The findings suggest that the fQ value strongly influences the rate of intestinal metabolism (Fp and Fsys) and indirectly affects the rate of liver metabolism due to substrate sparing effect. Thus, the fQ value in the intestinal flow models pose serious implications on the interpretation of data on the first-pass effect and oral absorption of drugs.

INTRODUCTION

Compartmental models are no longer adequate to address effects of permeability barriers (de Lannoy and Pang, 1986, 1987), intestinal and liver transporters and enzymes (Suzuki and Sugiyama, 2000a,b), and sequential metabolism within the intestine and liver (Pang and Gillette, 1979; Sun and Pang, 2010) during oral drug absorption (for reviews, see Pang, 2003; Pang et al., 2008; Fan et al., 2010; Pang and Dark, 2010; Chow and Pang, 2013). These aspects are especially pertinent when intestinal metabolic activity is substantial relative to that in the liver, and when different extents of induction/inhibition of intestinal and hepatic enzymes or transporters are the result of treatment with the culprit compound, which usually shows a higher induction/inhibition effect with oral administration (Fromm et al., 1996; Paine et al., 1996; Thummel et al., 1996; Eeckhoudt et al., 2002; Mouly et al., 2002; Fang and Zhang, 2010; Liu et al., 2010; Lledó-García et al., 2011; Zhu et al., 2011).

Over the past decade, there have been exciting advances made toward the development of physiologically relevant pharmacokinetic (PBPK) intestinal models to interrelate intestinal transporters, enzymes, and blood flow in the appraisal of their influence on intestinal (FI), liver (FHL), and oral systemic (Fsys or FabsFIFHL) availability. In this commentary, we revisited several physiologically based intestinal models that are associated with differential flow patterns: the traditional model (TM), in which the entire intestinal flow perfuses the enterocyte region; the segregated flow model (SFM), in which a low fractional flow (Qen) perfuses the enterocyte region (fractional flow, fQ or QGut/QPV is ≤0.3) (Cong et al., 2000); and the QGut model, in which

ABBREVIATIONS:
PBPK, physiologically based pharmacokinetic; FI or Fsys, intestinal availability; Fp, hepatic availability; Fsys, systemic availability; Fp, fraction absorbed; TM, traditional model; SFM, segregated flow model; Qen, low enterocyte flow; fQ, fractional flow rate to the enterocyte region; QPV, portal venous flow; QGut, effective flow; QPV, villous flow; P-gp, P-glycoprotein; po, oral; iv, intravenous; Cminmet, metabolic intrinsic clearance; P, precursor drug; Clintmet, H, metabolic intrinsic clearance for liver; Clntsec, intestinal secretion clearance; Clbili, liver biliary intrinsic clearance; Clint and Clint, influx and efflux intrinsic clearances; Clint, total intestinal intrinsic clearance; Clbili, total liver intrinsic clearance; fp, unbound fraction in blood; fQ, unbound fraction in intestine; fQ, unbound fraction in liver; AUC, area under the curve; k, absorption rate constant; kgl, luminal degradation rate constant; Papp, apparent permeability; Clp perm, drug permeability clearance; Peff, effective permeability; v, rate of intestinal removal; Vt, rate of hepatic removal; E, extraction ratio; Cint, arterial concentration; STM, segmental traditional model; SSFM, segmental segregated flow model; CPV, flow-averaged portal venous concentration.
the effective flow $Q_{out}$ that perfuses the enterocyte region is at best half the intestinal flow and close in value to the villous flow ($Q_{vill}$) (Yang et al., 2006, 2007; Gertz et al., 2010). These three intestinal models are viewed as competent to describe the immediate removal of the formed metabolite by excretion or sequential metabolism within the intestine and/or further processing by liver, for drugs and metabolites exhibiting varying permeability properties (Cong et al., 2000; Yang et al., 2006, 2007; Gertz et al., 2010; Sun and Pang, 2010). The models are more prepared to supply mechanistic insight into the pharmacokinetics of drugs and their metabolites and allow inclusion of transporters into different organ components (apical or basolateral membranes) to discriminate between the permeability properties of the drug and its formed metabolite in permitting or delimiting influx and efflux in drug and metabolite processing (Pang et al., 2008; Darwich et al., 2010; Galetin et al., 2010; Gertz et al., 2010; Rowland Yeo et al., 2010; Chow and Pang, 2013). By virtue of inclusion of transport and eliminatory events, these physiologically based models are able to more accurately describe the net appearance of the formed metabolite into the systemic circulation, because metabolite levels can be drastically reduced as a result of sequential metabolism (Pang and Gillette, 1979).

Intestinal PBPK models have been incorporated into whole body PBPK modeling. The semi-PBPK model proposed by Hall and colleagues (Quinney et al., 2008; Zhang et al., 2009; Quinney et al., 2010) resembles the TM-PBPK and features the intestine and liver tissues separately while minimizing the number of other tissues involved, retaining characteristics of the intestine and liver to describe metabolism, transport, and binding. The semi-PBPK model has been used to describe midazolam inhibition by intestinal and hepatically formed metabolites, N-desmethyl-diltiazem from diltiazem in humans (Zhang et al., 2009), and hydroxyitraconazole from itraconazole in rats (Quinney et al., 2008), and in the estimation of the contribution of the intestine (30–40%) in furamidine formation from pafuramidine in a prodrug-drug relationship in rats, then humans (Yan et al., 2012). Chow et al. (2011) used the combined TM-PBPK and SFM-PBPK models to predict the 1.8- and 2.6-fold induction of brain and kidney P-glycoprotein (P-gp) protein expression with the vitamin D receptor ligand, 1α,25-dihydroxyvitamin D$_3$, respectively, and demonstrated a superior fit with the SFM-PBPK model in explaining the P-gp-mediated excretion of digoxin. In the perfused rat intestine preparation in which the intestine is the only eliminating tissue, the SFM was found to be superior to the TM in describing morphine glucuronidation (Cong et al., 2000) and digoxin excretion by the P-glycoprotein under induced and noninduced states (Liu et al., 2006). In this commentary, we appraised how these intestinal flow models differed by examining the effects of enterocytic flow on $F_{sys}$ and, in turn, $F_{sys}$ and the extents of intestinal and liver first-pass removal with use of simulations.

**Theoretical: The Intestinal Flow Models**

The TM and SFM. Historically, the TM and SFM were first introduced by Cong et al. (2000) to offer an explanation of the higher extent of intestinal metabolism of erythromycin (Lown et al., 1995) and midazolam (Paine et al., 1996) in humans, and enalapril hydrolysis (Pang et al., 1985) and morphine glucuronidation in thevascularily perfused rat intestine preparation (Doherty and Pang, 2000) between oral (po) versus intravenous (iv) dosing of drugs. Both models describe the effects of protein binding, enzymes for parallel and sequential pathways, and passive diffusion and/or transporter-driven permeation in metabolically and transport-competent enterocytes (Cong et al., 2000). In this model, one or more metabolic pathways, denoted as the metabolic intrinsic clearances, $CL_{int,met1}$ and $CL_{int,met2}$, for the intestine may exist for precursor drug (P), and, similarly, $CL_{int,met1,H}$ and $CL_{int,met2,H}$ denote parallel metabolic pathways for the liver (Fig. 1). Drug secretion is represented by the $CL_{out,sec}$ for the intestinal secretion intrinsic clearance and $CL_{out,sec,H}$ for the liver biliary intrinsic clearance. Figure 1A denotes intestinal removal only, whereas Fig. 1B denotes both intestinal and liver removal; there is no elimination from other organs and tissues, which are lumped as highly and poorly perfused tissues. The influx and efflux clearances are denoted as $CL_{int,i}$, $CL_{int,e}$, $CL_{liver,i}$, and $CL_{liver,e}$ for the intestine (Fig. 1B, superscript I) and liver (Fig. 1B, superscript H); the unbound fractions in blood, intestine, and liver are denoted as $f_{I}$, $f_{e}$, and $f_{H}$, respectively (although not shown in Fig. 1 for the sake of simplification). The single, significant difference between the TM and SFM is the flow pattern for perfusion of tissue regions of the small intestine. The SFM emphasizes a low flow ($f_{Q} = 0.05–0.3\times$ total intestinal flow) that perfuses the enterocyte region, and the remaining flow ($[1-f_{Q}]Q_{PV}$) is shunted to the serosal or nonactive region (Fig. 1). This segregated flow pattern contrasts with the TM that describes the entire flow being able to reach the enterocyte or the total intestinal tissue, that is, $f_{Q} = 1$ (Cong et al., 2000).

Explicit solutions for the area under the curves (AUCs) for the TM- and SFM-PBPK models that feature the intestine as the only eliminating organ (Fig. 1A) were provided by Sun and Pang, (2009, 2010). These AUCs could be further modified by consideration of protein binding (unbound fractions $f_{I}$ and $f_{e}$) for po and iv dosing:

$$AUC_{po} = \frac{F_{abs}Dose_{po}CL_{d1}}{f_{Q}CL_{d1}[CL_{int,met1} + CL_{int,met2} + (1 - F_{abs})CL_{int,sec}]}$$

and

$$AUC_{iv} = \frac{Dose_{iv}(f_{Q}Q_{PV}CL_{d2} + (f_{I}CL_{d1} + f_{Q}Q_{PV})CL_{int,met2} + CL_{int,met1} + (1 - F_{abs})CL_{int,sec})}{f_{Q}Q_{PV}CL_{d2}[CL_{int,met1} + CL_{int,met2} + (1 - F_{abs})CL_{int,sec}]}$$

In eqs. 1 and 2, the $f_{I}$ term appears next to $CL_{int,met1}$ and $CL_{int,met2}$ is also recognized that tissue binding effects are apparently nonoperative because the $f_{I}$ term cancels out in both the numerator and denominator. The difference in flow between the TM and SFM is denoted by $f_{Q}$, the fraction of $Q_{PV}$ that perfuses the enterocyte region; for TM, $f_{Q} = 1$, whereas for SFM, $f_{Q} = 0.05$ to 0.3. The flow term is absent for $AUC_{po}$, but present in $AUC_{iv}$.

Accordingly, the $F_{I}$ and $F_{sys}$ is as follows:

$$AUC_{iv}/Dose_{iv} = F_{sys} = F_{abs}F_{I}$$

$$AUC_{po}/Dose_{po} = F_{sys} + F_{abs}F_{I}$$

Likewise, the AUCs for the TM- and SFM-PBPK models that feature both the intestine and liver as eliminating organs (Fig. 1B) have been solved (Sun and Pang, 2010), and their ratio, after consideration given to protein binding, is as follows:

$$AUC_{iv}/Dose_{iv} = AUC_{po}/Dose_{po} = F_{sys} = F_{abs}F_{I}$$

$$F_{sys} = \frac{f_{Q}Q_{PV}CL_{d2} + (f_{Q}Q_{PV} + f_{I}Q_{PV})CL_{int,met2} + (1 - F_{abs})CL_{int,sec}}{f_{Q}Q_{PV}CL_{d2}[CL_{int,met1} + CL_{int,met2} + (1 - F_{abs})CL_{int,sec}]}$$

Again, tissue binding effects are nonoperative because $f_{I}$ and $f_{e}$ or the tissue unbound fractions for the intestine and liver, cancel
The Fabs term has been reported to be highly correlated to gastrointestinal transit and degradation (Lin et al., 1999; Sun and Kadono et al., 2010). Apical secretion mediated via the CLint,sec,I was related to the permeability of drug, Papp (Zhu et al., 2002; Corti et al., 2006; Chow and Pang, 2013). As emphasized for the SFM, the partial flow suggests a bypass of enterocytes for drugs entering the intestinal tissue from the systemic circulation, whereas by design, drug given orally necessitates passage of the entire absorbed amount through the enterocyte region. This scenario would lead to a greater extent of intestinal removal for the drug.
given orally versus when the drug is given intravenously (Cong et al., 2000), rendering “route-dependent intestinal removal.”

The QGut Model. Yang et al. (2007) constructed the “QGut model” based on an effective flow, Qvilli, to the enteroocyte region, by relating this effective QGut to the intestinal availability, F2 or F3, in their terminology. The equation for F3 is based analogously to the equation for hepatic availability (F1h), according to the well stirred liver model (Pang and Rowland, 1977), where F2 is the unbound fraction of drug in intestinal tissue and CLint,sec,I, the total, intestinal intrinsic clearance that encompasses both secretion and metabolism.

\[ F3 = \frac{QGut}{Qvilli + fICLint,sec,I} \]  

The QGut is a hybrid term derived from the actual Qvilli [18 l/h or 300 ml/min (Gertz et al., 2010), representing ~48.4% of the total intestinal flow (assumed to equal the portal venous flow or Qpv, ~620 ml/min) (Valentin, 2002; Yang et al., 2006, 2007)] and drug permeability clearance (CLperm), a parameter that is normally estimated as the area x effective permeability (Pe) assessed from perfused (human) jejunal studies, from Caco-2 cell Papp or based on physicochemical data such as hydrogen bond donors and polar surface area. The QGut value of midazolam, a drug with high apparent permeability, was estimated to be 16.6 l/h, a value that is 92% of the value of Qvilli (Gertz et al., 2010).

\[ QGut = \frac{QvilliCLperm}{Qvilli + CLperm} \]  

For a drug that is highly permeable, CLperm >> Qvilli, it may be deduced that QGut = Qvilli. Upon substitution of eq. 6 into eq. 5, the following is obtained:

\[ F3 = \frac{QvilliCLperm}{Qvilli + CLperm} \]  

As originally conceived by Yang et al. (2007), the CLperm term stands collectively for \( CL_{d1} \) and \( CL_{d2} \), but should be replaced appropriately by either \( CL_{d1} \) or \( CL_{d2} \). Upon comparison of eq. 7 with eq. 3, the CLperm terms for the QGut model could now be assigned. By analogy to eq. 3, it is further recognized that \( fICLint,sec,I \) is equivalent to the composite term, \( fICLint,sec,I = (Qvilli + (Qvilli + CLperm) \times (1-Fabs)CLint,sec,I) \). The term \( fICLint,sec,I \) in the QGut model which represents the summed unbound metabolic and secretory intrinsic clearances, fails to consider the intestinal secretion followed by reabsorption of the secreted material in the lumen. Upon consideration of all these missed events:

\[ F3 = \frac{QvilliCLperm}{QvilliCLperm + (Qvilli + CLperm)CLint,sec,I} \]  

\[ CL_{d1} \]  

\[ CL_{d2} \]  

\[ (Qvilli + fICLint,sec,I)CLint,sec,I + (1-Fabs)CLint,sec,I \]  

\[ CL_{d2} \]  

\[ (Qvilli + fICLint,sec,I)CLint,sec,I + (1-Fabs)CLint,sec,I \]  

\[ CL_{d2} \]  

\[ (Qvilli + fICLint,sec,I)CLint,sec,I + (1-Fabs)CLint,sec,I \]  

eq. 8 is obtained for the QGut model, in an equivalent format as that for the TM and the QGut model. The \( fQ_{QPV} \) term for the SFM is equivalent to the \( Qvilli \) term of the QGut model (300 ml/min), which describes a partial flow (\( fQ = 0.484 \)) perfusing the enterocyte region.

**Results**

Comparison of \( fQ \). A proper comparison of these models has not been made in any rigorous fashion, especially in regard to \( fQ \) on F3. The starting point of the comparison is \( fQ \), being of a low value (~0.05–0.3) for the SFM, ~0.5 (Qvilli/Qpv = 0.484) for the QGut model, and highest (1.0) for the TM. We feel that the \( fQ \) term could serve as an important variable for selection of the most appropriate model to best describe the intestine. Upon perusal of the literature, estimates of QGut according to eq. 2 for various drugs range from 2.4, 5.7, 8.6, to 16.6 l/h, corresponding to 6.5 to 43% of the total intestinal flow, with good predictions for midazolam but poor estimation of F3 (or F1h) for saquinavir in vivo (Gertz et al., 2010). Some of these \( fQ \) values for the QGut model are higher than the \( fQ \) values of 0.07, 0.024, and 0.2 estimated from fits of the SFM to the data on benzoic acid (Cong et al., 2001), morphine (Cong et al., 2000), and digoxin (Liu et al., 2006), respectively, from vascularily perfused rat small intestine preparations. For digoxin, which is mainly excreted unchanged in the mouse in vivo, a value of 0.16 was found for \( fQ \) (Chow et al., 2011). The \( fQ \) terms, whether for the SFM or for QGut model, are less than unity (Gertz et al., 2010; Chow and Pang, 2013), with \( fQ \) values being higher (>0.3) for the QGut model. Values of \( fQ \) for the SFM are lower and correspond better with published evidence that suggests segregated flows for the small intestine, and that a small fraction of flow (5–30%) perfuses the active, mucosal region (Granger et al., 1980).

**Simulation of F3**. Equation 1 for the TM and SFM, which consider the intestine as the only eliminating organ, lacks any of the flow terms and suggests that AUCpo is identical among the TM, QGut model, and SFM, whereas the AUCiv intended for the TM/SFM (eq. 2) consists of the flow term, \( fQ_{QPV} \) for SFM and TM, and Qvilli for the QGut model, by analogy. Thus, different AUCiv values for the QGut model and the SFM result when the flow term is replaced by the appropriate flow rate, \( fQ_{QPV} \) or \( fQ_{QPV} \). Because the rate of intestinal metabolism is dependent on the flow rate for delivery of substrate, it may be concluded that, when a smaller flow reaches the enterocyte region, a smaller intestinal removal rate results with systemic delivery. The ranking of the intestinal removal rate is SFM < QGut model < TM after intravenous dosing. The lower flow rate stipulated by the SFM in bringing the substrate into enterocyte region yields a higher AUCiv (ranking for AUCiv: SFM > QGut model > TM) and consequently a lower F3 for the SFM compared with the QGut model and TM for given CLint,met,1 values. This view is supported by the simulations (Fig. 2A). The ranking of F3 was SFM < QGut model < TM.

It is further observed that the solutions for F3 are identical for the scenario in which the intestine is the only eliminating organ (eq. 3) and when the intestine and liver are both eliminating organs (eq. 4). These patterns for F3 (Fig. 2A) are translated into Fsys for any given F3H (= 0.1, 0.5, or 0.9; Fig. 2B). Again, the simulated patterns are consistent with the view that a decreased intestinal extraction ratio is accompanied by an increase in mesenteric flow (Chen and Pang, 1997; Chalasani et al., 2001; Yang et al., 2007; Chow and Pang, 2013); the lower intestinal removal rate due to lower enterocyte flows would result in higher hepatic processing, as observed experimentally by Chen and Pang (1997).

**Changing CL_{d1} or CL_{d2} on F3**. When we further examined the effects of the basolateral influx (CL_{d1}) or efflux (CL_{d2}) transport clearances for drugs that exhibit varying degrees of absorption (described by Fabs = 0.1, 0.5, and 1.0), all models show that F3 is attenuated when CL_{d1} is increased or when CL_{d2} is decreased (Fig. 3). Increasing the influx basolateral clearance (CL_{d1}) from low to high
(left column, from 1 to 5 and 20× blood flow; Fig. 3) would lead to lower F1 values, whereas upon increasing values of CLd2 from low to higher values [from 1 to 5× flow, middle column; then 20× flow, right column (Fig. 3)], higher F1 values are attained due to ability of the influxed drug to escape intestinal enzymes intracellularly. The FQ effects from the flow models are apparent again with the simulations, and the ranking for F1 values is SFM < QGut model < TM (Fig. 3).

**Contributions from Intestine and Liver to First-Pass Effect.** To assess the contributions from the intestine versus the liver in first-pass removal among these flow-intestinal models, we further simulated the rates predicted from the mass equations shown below (eqs. 9 and 10) that describe the rates of intestinal (vI) and hepatic (vH) removal. For estimation of the rates, there exists the need to define the flow-averaged portal venous concentration, $C_{PV}$, to account for the partial flow entering the enterocyte region, and for accurate prediction of the intestinal removal rate, $v_I$:

$$v_I = \frac{Q_{PV}C_A - Q_{PV}\bar{C}_{PV}}{Q_{PV}} = Q_{PV}C_A(1 - [f_0F_1 + (1 - f_0)])$$  \hspace{1cm} (9)

$$v_H = \frac{Q_{PV}\bar{C}_{PV}E_H + Q_{HA}C_AE_H}{Q_{PV}} = C_AE_H\left[\frac{f_0F_1}{Q_{PV}} + (1 - f_0)\right] + Q_{HA}$$  \hspace{1cm} (10)

Here, $E$ is the extraction ratio for the intestine or liver that equals (1-F), and $C_A$ is the arterial concentration. The fractional contributions by the intestine and liver may now be calculated.

The fractional contribution by intestine to the first-pass effect is as follows:

$$\frac{v_I}{v_I + v_H} = \frac{f_0Q_{PV}(1 - F_1)}{f_0Q_{PV}(1 - F_1) + E_H(Q_{PV}[f_0F_1 + (1 - f_0)] + Q_{HA})}$$  \hspace{1cm} (11)

and the fractional contribution by liver to the first-pass effect is as follows:

$$\frac{v_H}{v_I + v_H} = \frac{E_H(Q_{PV}[f_0F_1 + (1 - f_0)] + Q_{HA})}{f_0Q_{PV}(1 - F_1) + E_H(Q_{PV}[f_0F_1 + (1 - f_0)] + Q_{HA})}$$  \hspace{1cm} (12)
vH replaces fQQPV, in eqs. 9, 10, 12, and 13 for the QGut model, with fQ0.484. Again, substitution of fQ (1, 0.484, and 0.1 for TM, QGut model, and SFM, respectively) embedded in F1 or F2 (eq. 5) yields the corresponding fractional removal estimates. Accordingly, the lower intestinal removal rate (vI) predicted by the SFM due to the reduced flow rate results in a correspondingly higher contribution by the liver due to the substrate sparing effect of the intestine (Fig. 4). Whereas for TM, the greater intestinal contribution in removing the drug leads to a lesser removal contribution by the liver due to a substrate depleting effect of the intestine (Fig. 4). Predictions from the QGut model on the intestinal and liver contributions to first-pass removal fall in between those for the SFM and TM, and the patterns are similar when Fab0.1 or 0.9 (Fig. 4).

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Again, the predictions reveal that the fQ values in different intestinal models affect the contributions of the intestine and liver in the first-pass effect. For any given Clint,met1,I, this difference translates to ranking for the intestinal contribution to the first-pass effect as TM > QGut > SFM, and for the liver, the ranking is TM < QGut < SFM. These opposite trends in intestinal versus hepatic contributions to first-pass have been discussed by Xu et al. (1989) and Chen and Pang (1997), who attributed their observations to the anterior positioning of the intestine without recognizing the segregated flow effects. It must be commented that the effect of Fab is not apparent in altering the contributions of the intestine or liver in first-pass removal in these simulations; the Fab term affects only the reabsorption of the intestinally secreted drug (eqs. 3 and 4), which has been, for all intent and purpose, a minor pathway (Clint,sec1,I < 200 ml/min) relative to values of Clint,met2,I examined.

Effects of Binding. The mathematical manipulation reveals that tissue binding effects are canceled out because the unbound fraction terms in intestine (fI) or liver (fH) are absent in both the numerator and denominator. As seen from eqs. 3 and 4, only the fB term persists in the equations and is associated with the influx clearances, Cld1,I (superscripted I and H, respectively). Upon changing fB at three sets of Clint,met1,I values for the various models (Fig. 5), it could be seen that increased values of fB generally lower FI (Fig. 5). Exceedingly similar patterns are observed for Fab0.1 and 0.9.

Discussion

This examination reveals that fQ is the key issue in the prediction of F1 and contribution of both the intestine and liver to first-pass removal. The QGut model is similar to the SFM in many respects, except that a higher limit exists for fQ. The simulations, based on the various fQ values, show that the predicted intestinal availability of the QGut model falls between those of the TM and SFM models under varying conditions of efflux and influx clearances (Fig. 3). Decreased intestinal availabilities are expected.
with lower $f_Q$ values (Fig. 2), and this effect contributes to a greater proportion of first-pass extraction by the liver, the posterior organ (Fig. 4).

A major issue for the prediction of $F_I$ is the choice of the correct $f_Q$ value for intestinal models, especially for the $Q_{Gut}$ model. The problem that the intended $Q_{Gut}$ term is a hybrid function of $Q_{villi}$ and $CL_{perm}$ (as shown in eq. 7) could now be circumvented with use of eq. 8. Although literature reports for the $Q_{Gut}$ model suggest that $f_Q$ varies between 0.07 and 0.43, we suggest use of the unambiguous $Q_{villi}$ term or $f_Q/Q_{PV}$ ($f_Q = 0.484$) for the $Q_{Gut}$ model, with inclusion of the $CL_{d1}$ and $CL_{d2}$ terms in lieu of $CL_{perm}$ in a format similar to those for the SFM and TM (eq. 8) to define the fractional flow and the transport intrinsic clearances. This revelation implies that the effective flow rate to the enterocyte region ($f_Q = 0.484$) for the $Q_{Gut}$ model is higher than that for the SFM. Another revelation is that $f_CL_{int,I}$ in $Q_{Gut}$ model falls short of the more comprehensive term, $[CL_{int,met,I} + (1-F_{abs})CL_{int,sec,I}]$, in the prediction of $F_{abs}$ (or $F_I$ in our terms). This may be another reason why prediction prevails for some drugs that are P-gp substrates (Gertz et al., 2010). Indeed, improved estimation of $P_{eff}$ with use of a P-gp inhibitor seemed to improve the $F_I$ prediction of saquinavir (Gertz et al., 2011). The need for $f_I$ in the equation for the $Q_{Gut}$ model is questionable because the term cancels out even when the binding effects of intestinal tissue on efflux, metabolism, or excretion are taken into consideration.

Other theoretical modeling that considers heterogeneity of transporters and enzymes along the length of the small intestine, as in the segmental traditional (STM) and segmental segregated flow (SSFM) models (counterparts of TM and SFM), has revealed that metabolic heterogeneity strongly affects $F_I$ (Tam et al., 2003). Wu (2012) has recently commented, in a theoretical examination, that heterogeneity matters in predicting $F_{sys}$ after comparison of simulations from the TM-PBPK and SSFM-PBPK models on the systemic availability of the parent aglycone during the process of enterohepatic circulation of biliarily excreted glucuronides. The consideration of heterogeneity of transporters and enzymes on intestinal modeling in vivo surfaced much later, possibly due to the difficulty in obtaining population and length-averaged estimates on physiological dimensions of the lumen, surface area, flow, and enzymes and transporters in humans and animals (Badhan et al., 2009; Bruyère et al., 2010). Other compartmental models, when coupled with a refined description on the linear transfer kinetics of state properties of the drug (unreleased or solid form, undissolved or aggregate form, and dissolved or solution form), physicochemical properties ($pKa$, solubility, particle size, particle density, and permeability), physiological properties (gastric emptying, intestinal transit rate, intestinal metabolism, and luminal transport), and dosage factors (dosage form and dose), in the gastrointestinal tract show much improved predictions of drug kinetics (Agoram et al., 2001; Hendriksen et al., 2003), especially with inclusion of heterogeneity factors in the modeling (Bolger et al., 2009; Abusalal et al., 2012). However, the ability of many of the present models to fully
describe metabolite kinetics remains uncertain. We have noted that heterogeneity models such as the SSFM and STM (Tum et al., 2003), whether necessary or not, are more pertinent in cases of enzyme heterogeneity among the segments. In absence of metabolism by the intestine, we found that the STM and SSFM perform as well as the TM and SFM, as found for studies on the absorption of benzoic acid (Cong et al., 2001) and digoxin absorption and efflux by P-gp (Liu et al., 2006) in the vascularly perfused intestine preparation. The presence of metabolite data is an absolute necessity for the discrimination between the SFM and TM.

It can be concluded that the designated flow rate to the enterocyte region of the intestine, defined according to the different intestinal flow models, strongly affects $F_t$ and $F_{sys}$ and the proportions of intestinal and liver in first-pass removal. With the solved equations for the AUCs, it is apparent that predictions on the interplay between the SFM and TM, as found for studies on the absorption of benzoic acid.

$F_{abs} = 0.1$

$F_{abs} = 0.9$

Unbound Blood Fraction ($f_B$)