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Fraction of a dose absorbed estimation for structurally diverse low solubility compounds

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ABSTRACT

The purpose of the present study was to investigate the prediction accuracy of the fully mechanistic gastrointestinal unified theoretical (GUT) framework for in vivo oral absorption of low solubility drugs. Solubility in biorelevant media, molecular weight, log P_{oct}, pK_a, Caco-2 permeability, dose and particle size were used as the input parameters. To neglect the effect of the low stomach pH on dissolution of a drug, the fraction of a dose absorbed (*Fa*%) of undissociable and free acids were used. In addition, *Fa*% of free base drugs with the high pH stomach was also included to increase the number of model drugs. In total twenty nine structurally diverse compounds were used as the model drugs. *Fa*% data at several doses and particle sizes in humans and dogs were collated from the literature (total 110 *Fa*% data). In approximately 80% cases, the prediction error was within 2 fold, suggesting that the GUT framework has practical predictability for drug discovery, but not for drug development. The GUT framework appropriately captured the dose and particle size dependency of *Fa*% as the particle drifting effect was taken into account. It should be noted that the present validation results cannot be applied for salt form cases and other special formulations such as solid dispersions and emulsion formulations.

1. Introduction

Accurate prediction of in vivo oral absorption from in vitro data is one of the critical success factors in drug discovery and development (van de Waterbeemd and Gifford, 2003). Recently, the theoretical models of dissolution, nucleation, permeation and gastrointestinal transit were compiled as the gastrointestinal unified theoretical (GUT) framework (Sugano, 2009c). In the GUT framework, the physiological and drug parameters are explicitly taken into account in the mechanistic model equations. In addition, various states of drug molecules are explicitly taken into account such as free monomer and bile micelle bound species. This fully mechanistic approach enables integration of in silico and in vitro data to predict in vivo oral absorption of a drug (Sugano, 2010c; Sugano et al., 2006). In addition, it enables us to estimate the contribution of each primary process to the net oral absorption (Obata et al., 2005; Sugano et al., 2003). The GUT framework has been applied for predicting the fraction of a dose absorbed (*Fa*%) of wide variety of low permeability drugs (Obata et al., 2005; Sugano et al., 2002, 2003, 2006), as well as several low solubility drugs (Sugano, 2009a,d, 2010b,c). In addition, it was used to predict species differences, particle size dependency (including nano particles), dose dependency, the food effect and the stomach pH effect (Sugano, 2009d,f, 2010c; Sugano et al., 2010). These previous investigations suggested that the GUT framework has reasonable predictability for drug discovery. However, its predictability for a wide range of low solubility drugs has not been investigated. In the present study, 29 low solubility compounds with various dose strength and particle size were used to investigate the predictability of the GUT framework (total 110 *Fa*% data).

In the GUT framework, various physiological parameters such as the intestinal tube radius (R_{GI}), surface expansion by plicate and villi structure (*PE* and *VE*, respectively), intestinal transit time (T_{si}), the intestinal fluid volume (V_{GI}) and the unstirred water layer (UWL) thickness (h_{UWL}) are used. In the literature, little inconsistency was observed for many of these parameters. However, some of the physiological parameters such as V_{GI} and h_{UWL} have two to three fold variations in the literature values, depending on the methodology to obtain these values. To increase the prediction accuracy, these values should be more accurately estimated.

The oral absorption of a drug can be categorized as permeability, dissolution rate and solubility–permeability limited cases (PL, DRL and SL, respectively) (Table 1) (Sugano et al., 2007; Takano et al., 2008; Yu, 1999). The last one is further divided to solubility–epithelial membrane permeability limited cases (SL-E) and solubility–unstirred water layer (UWL) permeability limited cases (SL-U) (Sugano et al., 2010). In this article, the term "solubility–permeability limited" is used rather than "solubility

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Table 1
Oral absorption category and criteria.

Oral absorption category	Criteria
Dissolution rate limited (DRL)	$Dn < Pn/Do$ (If $Do < 1$, $Dn < Pn$)
Permeability limited (PL)	$Do < 1$, $Pn < Dn$
Solubility–epithelial membrane permeability limited (SL-E)	$Do > 1$, $Pn/Do < Dn$, $P'_{ep} < P_{UWL}$
Solubility–UWL permeability limited (SL-U)	$Do > 1$, $Pn/Do < Dn$, $P'_{ep} > P_{UWL}$

limited" to clearly indicate that the oral absorption of this case is determined as solubility × *permeability*, and estimation of permeability is of critical importance for this case (Sugano, 2009a). The uncertainty in V_{GI} has a large effect on that in the SL-E and SL-U cases, whereas it has little effect on oral absorption of PL and DRL cases. In addition, h_{UWL} affects the oral absorption in the SL-U cases. The particle drifting effect (PDE) was proposed in which the effect of drug particles in the UWL was taken into account (Sugano, 2010b,c).

In the present study, V_{GI} was first refined with a small set of drugs whose *Fa*% is specifically sensitive to the V_{GI} value, i.e., SL-E cases. The h_{UWL} and two parameters of the PDE were then optimized with SL-U cases. Finally, the overall predictability was investigated, including all cases of SL-E, SL-U and dissolution limited cases.

2. Methods

2.1. Theory

The fraction of a dose absorbed (*Fa*) was calculated based on the GUT framework as previously reported (Sugano, 2009c), and only briefly described in the following. Even though a dynamic multi-compartment model is provided in the GUT framework, an approximate analytical solution for the one compartment model (Eq. (1)) was used in this study because of its convenience for parameter optimization (Sugano, 2009b,c).

$$Fa = 1 - \exp\left(-\frac{1}{(1/k_{disso}) + (k_{perm}/Do)} T_{si}\right) = 1 - \exp\left(-\frac{1}{(1/Dn) + (Do/Pn)}\right) \quad \text{if } Do < 1, \quad Do = 1 \tag{1}$$

$$Pn = k_{perm} \cdot T_{si}, \quad Dn = k_{disso} \cdot T_{si}, \quad Do = \frac{Dose}{S_{dissolv} \cdot V_{GI}} \tag{2}$$

where k_{disso} and k_{perm} are the dissolution and permeation rate constants, respectively, *Pn*, *Dn* and *Do* are the permeation, dissolution and dose numbers, respectively (Oh et al., 1993), T_{si} is the transit time in the absorption site (small intestine), $S_{dissolv}$ is the solubility of a drug in the intestinal fluid, and V_{GI} is the fluid volume. To increase the accuracy of this approximate equation, prolonged duration of saturated concentration in the intestinal fluid (the remaining particle effect) and sequential first order correction were taken into account as previously reported (Sugano, 2009b). These corrections are basically a minor component in *Fa* calculation. The mean difference of calculated *Fa*% between the dynamic seven compartment model and Eq. (1) is less than 5% (The difference is within −12 to +18% range.) (Sugano, 2009b).

k_{disso} and k_{perm} are calculated from the drug and physiological parameters as,

$$k_{disso} = \frac{3D_{eff} \cdot S_{surface}}{\rho} \sum^{i} \frac{f_i}{r_{p,i}^2} \tag{3}$$

$$k_{perm} = \frac{2DF}{R_{GI}} \cdot P_{eff} \tag{4}$$

$$P_{eff} = \frac{PE}{(1/P'_{ep}) + (1/P_{UWL})} = \frac{PE}{(1/f_{mono} \cdot (f_0 \cdot P_{trans,0} + P_{para}) \cdot VE) + (1/((D_{eff}/h_{UWL}) + P_{WC}))} \tag{5}$$

where D_{eff} is the effective diffusion coefficient, $S_{surface}$ is the solubility of a drug at the surface of the drug particle, ρ is the true density of a drug, f_i is the fraction of a drug amount in a particle size bin (i), $r_{p,i}$ is the initial particle radius, *DF* is the degree of flatness of the gastrointestinal tube, R_{GI} is the radius of the small intestine, *PE* and *VE* are the surface area expansion coefficients by the plicate (fold) and villi structure, respectively, P_{ep} is the epithelial membrane permeability ($P'_{ep} = P_{ep} \times VE$), P_{UWL} is the UWL permeability, f_{mono} is the free monomer fraction, f_0 is the fraction of undissociated species which can be calculated from pK_a of a drug and the Henderson–Hasselbalch equation, h_{UWL} is the thickness of the UWL and P_{WC} is permeability through the UWL by water convection. $S_{surface}$ was set equal to $S_{dissolv}$ for most cases except the cases when the drug molecules exits >50% dissociated at pH 6.5. For dissociable compounds cases, the Mooney–Stella method and the modified Henderson–Hasselbalch equation was used to calculate the solid surface pH and solubility (Mooney et al., 1981a,b; Sugano, 2009c).

In the GUT framework, the dissolved drug concentration is defined as the sum of various molecular states in the gastrointestinal fluid. In this study, free monomer and bile micelle bound molecules were considered. The effective diffusion coefficient (D_{eff}) and f_{mono} can be expressed as,

$$D_{eff} = D_{mono} \cdot f_{mono} + D_{bm}(1 - f_{mono}) \tag{6}$$

$$f_{mono} = \frac{S_{blank}}{S_{dissolv}} \tag{7}$$

where S_{blank} is the solubility of a drug in a buffer without bile micelles, D_{mono} is the diffusion coefficient of monomer molecules and D_{bm} is the diffusion coefficient of bile micelle bound molecules calculated from the bile acid concentration as previously reported (Sugano, 2009c). D_{bm} of FaSSIF in the UWL was set to be three fold larger (Li et al., 1996). D_{mono} (Avdeef, 2010), $P_{trans,0}$ (Avdeef et al., 2005; Sugano, 2009a) and P_{para} (Obata et al., 2004; Sugano, 2009f; Sugano et al., 2002) were calculated as,

$$D_{mono}\,(\mathrm{cm^2/s}) = 9.9 \times 10^{-5} MW^{-0.453} \tag{8}$$

$$P_{trans,0}\,(\mathrm{cm/s}) = 2.36 \times 10^{-6} P_{oct}^{1.1} \tag{9}$$

$$P_{para}\,(\mathrm{cm/s}) = 3.9 \times 10^{-4} \cdot \frac{1}{MW^{1/3}} \cdot RK\left(\frac{MW^{1/3}}{8.46}\right) \times \left(f_0 + \sum^{z(z \neq 0)} f_z \cdot \frac{2.39 \cdot z}{1 - e^{-2.39 \cdot z}}\right) \tag{10}$$

$$RK(x) = (1 - x)^2(1 - 2.104 \cdot x + 2.09 \cdot x^3 - 0.95 \cdot x^5) \quad x < 1 \tag{11}$$

where P_{oct} is the octanol/water partition coefficient and z is the charge-valence of molecular species. *RK* is the Renkin function which represents the sieving effect of pores.

The particles drifting effect (PDE) was recently proposed (Sugano, 2010c), in which a reduction of the UWL thickness as the drug particles drifting into the UWL is taken into account. Considering the PDE, h_{UWL} is calculated as,

$$h_{UWL} = h_{fam} \cdot \left(1 - RK\left(\frac{r_{p,mean}}{R_{mucus}}\right)\right) + h_{pd} - \frac{1}{2} h_{pd} \cdot R_{SA} \quad R_{SA} \leq 1 \tag{12}$$

Table 2
Drug parameters.

Drug	MW	z[a]	pK_a	log P	Solubility (mg/mL)			Caco-2 ($\times 10^{-6}$ cm/s)	References
					pH 6.5	FaSSIF	FeSSIF		
Acyclovir	225	0	–	−1.7	2.5	2.5[d]	–	0.38	Matsson et al. (2005), Sawyer et al. (1988), Sugano et al. (2001)
Albendazole	265	0	4.2	3.1	0.00055	0.0021	–	–	Escher et al. (2008), Fagerberg et al. (2010)
Aprepitant	534	0	4.2[b]	4.8	0.0008	0.021[e]	–	–	Aprepitant (2009), Takano et al. (2008)
Atovaquone	367	0	–	5.1	0.00043	0.0024	–	–	Singh (2005), Vertzoni et al. (2004)
Chlorothiazide	265	0	–	−0.24	0.73	0.87	0.83	0.92	Avdeef (2003), Saitoh et al. (2004), Sugano et al. (2010)
Cilostazole	369	0	–	2.7	0.0063	0.0064, 0.008[e]	0.014[e]	–	Jinno et al. (2006)
Cinnarizine	369	+	7.45	5.7	0.0014	0.013, 0.021[e], 0.013[f], 0.021[e,f]	–	–	Fagerberg et al. (2010)
Danazol	337	0	–	4.5	0.0002	0.018, 0.020[e]	0.047	–	Glomme et al. (2006), Okazaki et al. (2008), Sugano (2009d)
Digoxin	780	0	–	1.3	0.016	0.017	–	1.3	Alsenz and Kansy (2007), Dzimiri et al. (1987), Matsson et al. (2005)
Dipyridamole	505	0	6.2	3.9	0.006	0.017, 0.024[e]	–	–	Glomme et al. (2006), Takano et al. (2006)
Efavirentz	316	0	–	4.1	0.01	0.194	–	–	Takano et al. (2006)
Felodipine	384	0	–	4.3	0.00086	0.077[e]	–	–	Glomme et al. (2006), Scholz et al. (2002)
Fenofibrate	362	0	–	5.2	0.0002	0.014	0.037	–	Buch et al. (2009), Hanafy et al. (2007)
FTI-2600	448	0	–	3.2	0.0037	0.033[e]	–	–	Takano et al. (2010)
Ganciclovir	255	0	–	−1.7	4.3	4.3[d]	–	0.23	Matsson et al. (2005), Yang et al. (2006)
Gefitinib	447	+	7.2	4.1	0.0041	0.085, 0.083[f]	–	–	Gefitinib (2009), Wilson et al. (2009)
Glibenclamide	494	–	5.9	3.1	0.0045	0.0046, 0.0027[f]	–	–	Fagerberg et al. (2010)
Griseofulvin	353	0	–	2.5	0.01	0.015, 0.018[e]	–	–	Glomme et al. (2006), Okazaki et al. (2008), Sugano (2009d)
Irbesartan	429	–	4.4	4.0[c]	0.11	0.21, 0.11[f]	0.29	127	Irbesartan (2009), Sugano et al. (2010), Tosco et al. (2008), Young et al. (2006)
Ivermectine	875	0	–	3.2	0.0007	0.12	–	–	Takano et al. (2006)
Ketoconazole	531	+	6.5	4.3	0.012	0.021, 0.027[e]	–	–	Avdeef (2003), Takano et al. (2006), Vertzoni et al. (2004)
Lobucavir	265	0	–	−1.2	0.8	0.8[d]	–	0.88	Matsson et al. (2005), Yang et al. (2006)
Nitrendipine	360	0	–	3.3	0.004	0.016	–	–	Takano et al. (2006)
Panadiplon	335	0	–	1.2[b]	0.077	0.085[d,e]	0.13[e]	–	Nishihata et al. (1993)
Phenitoin	252	0	–	2.5	0.039	0.043	0.059	–	Glomme et al. (2006)
Pranlukast	491	–	3.4	4.2[b]	0.0033	0.088, 0.086[f]	0.8, 0.8[f]	25	Kataoka et al. (2003), Sugano et al. (2010)
Spironolactone	417	0	–	3.3	0.03	0.042	–	–	Takano et al. (2006)
Tolfenamic acid	262	–	4.8	5.7	0.027	0.063, 0.040[f]	–	–	Fagerberg et al. (2010)

[a] Dominant charge at pH 6.5 (>50% dissociated cases were assigned as + or −).
[b] Calculated value (ACD/Labs Software V8.14).
[c] Calculated from pK_a and log $D_{pH\,7.4}$.
[d] Estimated from blank buffer solubility and log P.
[e] For dogs.
[f] Solid surface solubility calculated based on the Mooney–Stella method and modified Henderson–Hasselbalch equation.

$$h_{UWL} = h_{fam} \cdot \left(1 - RK\left(\frac{r_{p,mean}}{R_{mucus}}\right)\right) + \frac{1}{2} \cdot \frac{h_{pd}}{R_{SA}} \quad R_{SA} > 1 \tag{13}$$

$$R_{SA} = \frac{3 \cdot C_{pd} \cdot h_{pd} \cdot Dose}{V_{GI} \cdot \rho} \sum_i \frac{f_i}{r_{p,i}} \tag{14}$$

where h_{fam} is the thickness of the firmly adhered mucus layer, R_{mucus} is the nominal radius of the pore size of the mucus layer, R_{SA} is the ratio of the drug particle surface area in the UWL and the villi surface area, C_{pd} is the particle drifting coefficient, and h_{pd} is the thickness of the particle drift-able region defined as $h_{pd} = h_{UWL} - h_{fam}$. The $1 - RK$ term was introduced in this investigation to represent the particles penetrating into the firmly adhered mucus layer. R_{mucus} and C_{pd} were optimized in this investigation.

2.2. Drug and physiological parameters

log P_{oct}, pK_a, solubility and Caco-2 permeability (P_{app}) were obtained from the literature (Table 2). The solubility values in the fasted and fed state simulated intestinal fluid (FaSSIF and FeSSIF, respectively) were used as $S_{dissolv}$, as the surrogates of solubility in the real intestinal fluid (Galia et al., 1998). These fluids consist of taurocholate (TC) and lecithin (4:1) and the phosphate buffer (pH 6.5). The pH of FeSSIF was set to pH 6.5 as recent update (Jantratid et al., 2008; Kataoka et al., 2003). TC of 3 mM, 5 mM, 15 mM and 18 mM was used for fasted humans, fasted dogs, fed humans and fed dogs, respectively (Galia et al., 1998; Sugano, 2009d; Takano et al., 2008 and references therein). For these bile concentrations, D_{bm} was calculated to be 0.13, 0.56, 1.12 and 1.14×10^{-6} cm^2/s, respectively. D_{bm} at 3 mM bile concentration was multiplied 3 fold for P_{UWL} calculation considering the interaction with mucus (Li et al., 1996). ρ was set to 1.2 g/cm^3. In the case of lipophilic drugs (log $D_{oct,pH\,6.5} > 2$), P_{ep} was estimated from log P_{oct}, pK_a and MW because their permeability is expected to be UWL limited and the Caco-2 study with a standard condition often underestimate the permeability of highly lipophilic drugs due to the lack of receiver sink condition, a thick in vitro UWL (ca. 1500–3000 μm) (Krishna et al., 2001; Youdim et al., 2003) and other experimental artifacts (Sugano et al., 2009). When P_{eff} is mainly determined by the UWL, the prediction error of the P_{ep} value has little effect on P_{eff} estimation. For less lipophilic drugs (log $D_{oct,pH\,6.5} < 2$), P_{ep} was assumed to be identical to Caco-2 apparent permeability. In this study, drug particles were assumed to have a log-normal distribution with ln2 standard deviation with a mean radius of $r_{p,mean}$. Therefore, $\sum f_i/r_{p,i}$ and $\sum f_i/r_{p,i}^2$ becomes ca. $1.4/r_{p,mean}$ and $3.3/r_{p,mean}^2$, respectively. For several cases, the particle size data is not available in the literature, therefore, was estimated from the dissolution test data. Previously, estimation of particle size from the dissolution test data was shown to be appropriate (Avdeef et al., 2009). In these cases

Table 3
Predicted and observed *Fa*%.

Drug	Species	State	Dose (mg)	d50[a] (μm)	*Dn*	*Do*	*Pn*	Pred. *Fa*%	Type	Obs. *Fa*%	Method[b]	Reference
Acyclovir	Human	Fasted	200	50a	353.3	0.6	0.3	27	PL	29	(VI)	Interview form, Steingrimsdottir et al. (2000), Vergin et al. (1995)
Acyclovir	Human	Fasted	400	50	353.3	1.2	0.3	23	SL-E	21	(VI)	
Acyclovir	Human	Fasted	800	50	353.3	2.5	0.3	13	SL-E	12	(VI)	
Albendazole	Human	Fasted	1400	10	1.9	5142.8	46.0	1.9	SL-U	2.7	(II)	Rigter et al. (2004), Schipper et al. (2000)
Aprepitant	Dog	Fasted	20	0.2	9434.5	51.4	48.1	82	SL-U	57	(III)	Takano et al. (2008), Wu et al. (2004)
Aprepitant	Dog	Fasted	20	2	94.3	51.4	6.6	21	SL-U	33	(II)	
Aprepitant	Dog	Fasted	20	5	15.1	51.4	3.7	12	SL-U	28	(II)	
Aprepitant	Dog	Fasted	20	26	0.6	51.4	2.7	7	SL-U	18	(II)	
Atovaquone	Human	Fasted	500	0.3	1468.2	1607.1	242.1	33	SL-U	39	(VI)	The electronic Medicines Compendium Wellvone 750 mg; Dixon et al. (1996), Freeman et al. (1998), Rolan et al. (1994)
Atovaquone	Human	Fasted	1000	0.3	1468.2	3214.2	311.3	23	SL-U	30	(VI)	
Atovaquone	Human	Fasted	1500	0.3	1468.2	4821.3	344.2	18	SL-U	17	(VI)	
Chlorothiazide	Human	Fasted	50	50	96.1	0.4	0.6	47	PL	56	(I)	Dressman et al. (1984), Welling and Barbhaiya (1982)
Chlorothiazide	Human	Fasted	500	50	96.1	4.4	0.6	17	SL-E	15	(I)	
Chlorothiazide	Human	Fed	500	50	97.6	3.9	0.7	19	SL-E	29	(I)	
Cilostazole	Dog	Fasted	100	0.22	21476.3	675.0	401.1	76	SL-U	100	(III),(VI)	Bramer and Forbes (1999), Jinno et al. (2006)
Cilostazole	Dog	Fasted	100	13	6.2	675.0	29.8	9	SL-U	20	(III),(VI)	
Cilostazole	Dog	Fasted	100	2.4	180.5	675.0	88.1	27	SL-U	21	(III),(VI)	
Cilostazole	Dog	Fed	100	0.22	25318.8	321.4	240.8	82	SL-U	95	(III),(VI)	
Cilostazole	Dog	Fed	100	13	7.3	321.4	17.8	11	SL-U	32	(III),(VI)	
Cilostazole	Dog	Fed	100	2.4	212.7	321.4	53.9	31	SL-U	75	(III),(VI)	
Cilostazole	Human	Fasted	50	10	17.8	60.3	20.8	47	SL-U	40	(II)	
Cilostazole	Human	Fasted	100	10	17.8	120.5	22.9	31	SL-U	31	(II)	
Cinnarizine	Dog	Fasted	25	25	0.8	64.3	3.1	7	SL-U	5	(IV),(VI)	Ogata et al. (1986), Yamada et al. (1990)
Cinnarizine	Human	Fasted	25	25	0.7	14.8	4.8	24	SL-U	27	(IV)	
Cinnarizine	Human	Fasted	25	60	0.1	14.8	4.8	9	DRL	13	(IV)	
Danazol	Dog	Fasted	2	5	11.9	5.4	2.4	43	SL-U	30	(II)	Charman et al. (1993), Liversidge and Cundy (1995), Sunesen et al. (2005), Takano et al. (2008)
Danazol	Dog	Fasted	20	5	11.9	54.0	3.3	11	SL-U	12	(II)	
Danazol	Dog	Fasted	20	229	0.0	54.0	2.3	0.35	DRL	2	(II)	
Danazol	Dog	Fasted	200	0.16	11582.9	540.0	127.2	43	SL-U	77	(II)	
Danazol	Dog	Fasted	200	10	3.0	540.0	8.3	3	SL-U	4.8	(II)	
Danazol	Human	Fasted	100	4.46	7.7	42.9	4.0	15	SL-U	18	(II),(III)	
Danazol	Human	Fed	100	4.46	111.9	13.7	6.4	52	SL-U	58	(II),(III)	
Digoxin	Human	Fasted	0.5	7	65.8	0.2	1.0	62	PL	78	(II)	Jounela et al. (1975)
Digoxin	Human	Fasted	0.5	13	19.1	0.2	1.0	60	PL	96	(II)	
Digoxin	Human	Fasted	0.5	102	0.3	0.2	1.0	10	DRL	37	(II)	
Dipyridamole	Human	Fasted	50	75	0.3	22.7	8.0	16	DRL	36	(IV)(VI)	Bjornsson and Mahony (1983), Russell et al. (1994), Zhou et al. (2005)
Dipyridamole	Dog	Fasted	75	75	0.2	166.0	4.6	3	SL-U	11	(IV)	
Efavirentz	Human	Fasted	600	3	444.4	23.9	20.0	75	SL-U	82	(III)	FDA approval document for sustiva; Gao et al. (2007)
Efavirentz	Human	Fasted	1200	3	444.4	47.7	27.4	65	SL-U	59	(III)	
Felodipine	Dog	Fasted	3	8	17.9	2.1	2.4	66	SL-U	72	(II)	Scholz et al. (2002)
Felodipine	Dog	Fasted	3	125	0.1	2.1	2.3	4	DRL	5	(II)	
Fenofibrate	Human	Fasted	145	0.4	811.0	79.9	28.6	50	SL-U	70	Other[c]	Guivarc'h et al. (2004), Sauron et al. (2006), Zhu et al. (2010)
Fenofibrate	Human	Fasted	200	2.2	26.8	110.2	8.9	15	SL-U	51	Other	
Fenofibrate	Human	Fed	67	2.2	364.0	11.6	7.6	63	SL-U	84	Other	
Fenofibrate	Human	Fed	145	0.4	11010.5	25.2	57.8	100	SL-U	79	Other	
Fenofibrate	Human	Fed	200	2.2	364.0	34.7	16.5	57	SL-U	72	Other	
FTI-2600	Dog	Fasted	30	1	931.0	49.7	21.4	55	SL-U	28	(II)	Takano et al. (2010)
Ganciclovir	Human	Fasted	500	50	574.1	0.9	0.2	18	PL	5.6	(VI)	Spector et al. (1995)
Ganciclovir	Human	Fasted	750	50	574.1	1.3	0.2	14	SL-E	4.5	(VI)	
Ganciclovir	Human	Fasted	1000	50	574.1	1.8	0.2	10	SL-E	4.5	(VI)	
Ganciclovir	Human	Fasted	1250	50	574.1	2.2	0.2	9	SL-E	2.6	(VI)	

Table 3 (*Continued*)

Drug	Species	State	Dose (mg)	d50[a] (μm)	*Dn*	*Do*	*Pn*	Pred. *Fa*%	Type	Obs. *Fa*%	Method[b]	Reference
Gefitinib	Human	Fasted	250	30	1.6	22.7	4.0	21	SL-U	39	(III),(IV),(VI)	Interview form, Bergman et al. (2007), Tashtoush et al. (2004)
Glibenclamide	Human	Fasted	5	50	0.3	8.4	16.8	22	DRL	45	(I)	
Griseofulvin	Dog	Fasted	2	7	35.8	6.0	7.5	81	SL-U	85	(II)	Ahmed et al. (2008), Chiou and Riegelman (1971), Takano et al. (2008)
Griseofulvin	Dog	Fasted	20	118	0.1	60.0	7.4	7	SL-U	2.9	(II)	
Griseofulvin	Dog	Fasted	20	7	35.8	60.0	10.7	28	SL-U	46.9	(II)	
Griseofulvin	Human	Fasted	125	4	181.8	64.3	28.8	57	SL-U	45	(III)	
Griseofulvin	Human	Fasted	500	4	181.8	257.1	78.5	49	SL-U	43	(I)	
Irbesartan	Human	Fasted	25	20	39.8	0.9	9.4	100	PL	99	(II)(VI)	Interview form, Hirlekar et al. (2009), Vachharajani et al. (1998)
Irbesartan	Human	Fasted	50	20	39.8	1.8	9.5	100	SL-U	83	(II)(VI)	
Irbesartan	Human	Fasted	100	20	39.8	3.7	9.9	100	SL-U	75	(II)(VI)	
Irbesartan	Human	Fasted	150	20	39.8	5.5	10.2	91	SL-U	71	(II)(VI)	
Irbesartan	Human	Fasted	200	20	39.8	7.3	10.6	86	SL-U	64	(II)(VI)	
Irbesartan	Human	Fasted	300	20	39.8	11.0	11.6	78	SL-U	78	(II)(VI)	
Irbesartan	Human	Fasted	600	20	39.8	22.0	15.8	69	SL-U	59	(II)(VI)	
Irbesartan	Human	Fasted	900	20	39.8	33.1	19.8	65	SL-U	54	(II)(VI)	
Irbesartan	Human	Fed	25	20	62.2	0.6	8.1	100	PL	83	(II)(VI)	
Irbesartan	Human	Fed	300	20	62.2	6.7	9.5	85	SL-U	90	(II)(VI)	
Ivermectine	Human	Fasted	6	25	1.2	0.4	2.8	52	DRL	54	(II)(III)	Interview form, FDA approval document for ivermectin; Guzzo et al. (2002), Takano et al. (2006)
Ivermectine	Human	Fasted	12	25	1.2	0.8	2.8	52	DRL	52	(II)(III)	
Ivermectine	Human	Fasted	15	25	1.2	1.0	2.8	52	DRL	51	(II)(III)	
Ivermectine	Human	Fasted	30	25	1.2	1.9	2.8	53	DRL	53	(II)(III)	
Ivermectine	Human	Fasted	60	25	1.2	3.9	2.8	43	SL-U	46	(II)(III)	
Ivermectine	Human	Fasted	90	25	1.2	5.8	2.9	36	SL-U	30	(II)(III)	
Ivermectine	Human	Fasted	120	25	1.2	7.7	2.9	31	SL-U	35	(II)(III)	
Ketoconazole	Human	Fasted	200	200	0.1	73.5	11.1	5	DRL	6	(II)	Lelawongs et al. (1988), Zhou et al. (2005)
Ketoconazole	Dog	Fasted	200	200	0.0	400.0	6.3	2	SL-U	3.3	(IV)	
Lobucavir	Human	Fasted	20	50	105.0	0.2	0.7	51	PL	48	(VI)	Yang et al. (2006)
Lobucavir	Human	Fasted	70	50	105.0	0.7	0.7	51	PL	53	(VI)	
Lobucavir	Human	Fasted	200	50	105.0	1.9	0.7	31	SL-E	42	(VI)	
Lobucavir	Human	Fasted	400	50	105.0	3.9	0.7	21	SL-E	28	(VI)	
Lobucavir	Human	Fasted	700	50	105.0	6.7	0.7	14	SL-E	14	(VI)	
Nitrendipine	Human	Fasted	20	10	12.1	9.6	7.3	65	SL-U	76	(II)	Mikus et al. (1987), Takano et al. (2006)
Panadiplon	Dog	Fasted	10	9	161.5	6.4	7.7	81	SL-U	84	(VI)	Nishihata et al. (1993)
Panadiplon	Dog	Fasted	10	25	20.9	6.4	7.3	77	SL-U	77	(VI)	
Panadiplon	Dog	Fasted	10	100	1.3	6.4	7.1	51	SL-U	25	(VI)	
Panadiplon	Dog	Fed	10	9	176.3	3.6	5.6	84	SL-U	100	(VI)	
Panadiplon	Dog	Fed	10	25	22.9	3.6	5.4	81	SL-U	91	(VI)	
Panadiplon	Dog	Fed	10	100	1.4	3.6	5.3	56	DRL	35	(VI)	
Phenitoin	Human	Fasted	280	4	819.7	50.2	81.3	95	SL-U	81	(II)(VI)	Hamaguchi et al. (1993), Lund et al. (1974), Mizuno et al. (2003), Yakou et al. (1984)
Phenitoin	Human	Fasted	200	50	5.2	35.9	22.0	56	SL-U	60	(II)(VI)	
Phenitoin	Human	Fasted	350	190	0.4	62.8	21.2	18	SL-U	14	(II)(VI)	
Phenitoin	Human	Fed	350	190	0.4	38.5	16.9	21	DRL	31	(II)(VI)	
Pranlukast	Human	Fasted	50	2	309.6	4.4	0.7	18	SL-E	20	Other[d]	Interview form, Brocks et al. (1996, 1997), Nakajima et al. (1993)
Pranlukast	Human	Fasted	100	2	309.6	8.8	0.7	11	SL-E	13	Other	
Pranlukast	Human	Fasted	300	2	309.6	26.3	0.8	5	SL-E	7.2	Other	
Pranlukast	Human	Fasted	600	2	309.6	52.6	0.8	3	SL-E	5.0	Other	
Pranlukast	Human	Fed	112.5	2	9408.9	0.9	0.1	8	PL	12	Other	
Pranlukast	Human	Fed	225	2	9408.9	1.8	0.1	5	SL-E	11	Other	
Pranlukast	Human	Fed	300	2	9408.9	2.4	0.1	4	SL-E	11	Other	
Pranlukast	Human	Fed	337.5	2	9408.9	2.7	0.1	4	SL-E	7.1	Other	
Pranlukast	Human	Fed	450	2	9408.9	3.6	0.1	3	SL-E	12	Other	
Pranlukast	Human	Fed	562.5	2	9408.9	4.5	0.1	2	SL-E	9.8	Other	
Pranlukast	Human	Fed	675	2	9408.9	5.4	0.1	2	SL-E	7.6	Other	
Spironolactone	Human	Fasted	200	10	80.8	36.7	21.2	64	SL-U	58	(III)	Barber et al. (1998), Overdiek and Merkus (1986)
Tolfenamic acid	Human	Fasted	200	6	159.5	24.5	24.5	81	SL-U	60	(VI)	Neuvonen and Kivisto (1988), Pedersen (1994), Pentikaeinen et al. (1981)
Tolfenamic acid	Human	Fasted	100	18	17.7	12.2	12.4	77	SL-U	82	(VI)	
Tolfenamic acid	Human	Fasted	200	18	17.7	24.5	13.7	60	SL-U	59	(VI)	

Table 3 (*Continued*)

Drug	Species	State	Dose (mg)	d50[a] (μm)	*Dn*	*Do*	*Pn*	Pred. *Fa%*	Type	Obs. *Fa%*	Method[b]	Reference
Tolfenamic acid	Human	Fasted	400	18	17.7	49.0	17.8	48	SL-U	61	(VI)	
Tolfenamic acid	Human	Fasted	800	18	17.7	98.0	31.0	44	SL-U	68	(VI)	

[a] Mean diameter (volume based). For acyclovir, chloothiazide, ganciclovir and lobucavir, the particle size was assumed to be 50 μm. Predicted *Fa%* did not depend on the particle size for these compounds. For cinnarizine, dipyridamole, gefitinib, ivermectine, ketoconazole, and nitrendipine, the particle size was estimated from the dissolution data.

[b] The method used to estimate *Fa%* (see text for detail).

[c] Estimated using the PK of acid parent drug.

[d] Estimated from the total metabolite amount in urine and the unchanged drug in the feces.

(see foot note of Table 3), the prediction process is a hybrid of prediction from the dissolution test and other in vitro data as the prediction error related to dissolution is corrected as the nominal particle size.

The following physiological parameters were used: $DF = 1.7$, $VE = 10$ and $h_{fam} = 15$ μm for both humans and dogs; $PE = 3$ and 1, $R_{GI} = 1.5$ and 0.5 cm, and $T_{si} = 3.5$ and 2 h, for humans and dogs, respectively (Atuma et al., 2001; DeSesso and Jacobson, 2001; DeSesso and Williams, 2008; Sugano, 2009d). V_{GI} of dogs was estimated as body weight normalized against that of humans (body weight = 70 and 10 kg for humans and dogs, respectively). V_{GI} in the fed state was set to 1.2 fold larger than that in the fasted state (Sugano et al., 2010). R_{mucus}, C_{pd}, and h_{UWL} were assumed to be the same between humans and dogs.

2.3. Fa% data

Twenty nine structurally diverse drugs were used as the model drugs. In vivo *Fa%* data from standard immediate release formulation were obtained from the literature. To neglect the effect of the low stomach pH (ca. 1.5) on dissolution of a drug, *Fa%* of undissociable drugs, free acid drugs and free base drugs with the high pH stomach (pH > ca. 5) were used in this study. When *Fa%* was sited the literature, it was used as it is (shown as method (I) in Table 3). If *Fa%* was not sited in the literature, *Fa%* was calculated as previously reported by Takano et al. (2006), i.e.: relative bioavailability of solution vs solid form formulation (II), relative bioavailability in the fasted vs the fed state (especially when $Do < 1$ at the fed state) (III), relative bioavailability with the low/high pH stomach when $Do < 1$ in the stomach (for basic drugs) (IV), dose-normalized relative bioavailability at $Do < 1$ vs $Do > 1$ when the terminal elimination half life is consistent (V), and from absolute bioavailability (F) and hepatic clearance using $Fa = F/(1 - CL_h/Q)$ (VI). The method (II)–(V) is used for lipophilic compounds ($\log D_{oct} > 0.5$) as *Fa%* can be assumed to be 100% when there is no solubility/dissolution rate limitations (Yazdanian et al., 1998). Multiple methods are used to increase the reliability of clinical *Fa%* values when the data are available in the literature. *Fa%* data at several dose strengths and particle sizes in humans and dogs were collated from the literature (total 110 *Fa%* data).

2.4. Parameter optimization

The least square method was used for parameter optimization with the Excel solver function. V_{GI}, h_{UWL}, R_{mucus}, and C_{pd}, were optimized in a stepwise manner using the model drugs whose *Fa%* is sensitive to these parameters (see Section 3 for details).

3. Results and discussion

Previously, V_{GI} and h_{UWL} were reported to be in the range of ca. 100–250 mL and ca. 90–300 μm, respectively. V_{GI} was reported to be 107 mL by the direct measurement using MRI imaging (Schiller et al., 2005), and 50–100 mL (Marciani et al., 2010), 202 mL in the post mortal intestine (McConnell et al., 2008), and 130 mL by indirect estimation from the PK profile fitting after intestinal administration of a few basic drugs (Sutton, 2009). h_{UWL} was reported to be ca. 300 μm from the P_{eff} values of glucose and antipyrin by using the Loc-I-Gut system and ca. 90 μm from the enzymatic metabolism rate of maltose (after normalized based on the fold surface). In the previous investigations of the GUT framework, 250 mL and 300 μm were tentatively used, as 250 mL was used in the biopharmaceutical classification system and 300 μm was estimated by the authentic permeability measurement method in conscious humans. These tentative values were found to result in a semi-quantitative prediction of *Fa%* for several SL-U cases such as danazol, griseofulvin, etc. (Sugano, 2009a,d). However, because these two parameters are conjugated for this type of drugs, validation with the SL-U cases only confirms the combination of V_{GI} and h_{UWL}, but not the absolute value of each parameter (in other words, V_{GI} and h_{UWL} are unidentifiable from the *Fa* of SU data since the errors in these parameters might cancel-out). Furthermore, the PDE was not taken into account in these reports of SL-U cases. In addition, for V_{GI} estimation, the PL and DRL cases are not suitable as *Fa%* of these cases is less sensitive to V_{GI}. The permeation rate constant (k_{perm}) is defined as k_{perm} = permeation clearance/V_{GI} = surface area/$V_{GI} \times P_{eff}$. Considering the tube shape of the small intestine, the surface area which is in contact with the intestinal fluid is in proportion to the intestinal fluid volume. Therefore, the ratio of surface area/V_{GI} becomes constant regardless of the fluid volume and is equal to $2/R_{GI} \times DF$. Therefore, to enable independent estimation for V_{GI} and h_{UWL}, V_{GI} was first refined by using the solubility–epithelial membrane limited cases (SL-E).

V_{GI} was refined using 4 SL-E absorption drugs, i.e., acyclovir, chlorothiazide, ganciclovir and lobucavir as follows. *Pn* was first back-calculated from clinical *Fa%* at dose strength of $Do < 1$ (i.e., at this dose, oral absorption becomes permeability limited) (cf. $Pn = -\ln(1 - Fa)$). The *Pn* values were 0.34, 0.82, 0.058 and 0.65, respectively. With these *Pn* values, V_{GI} was then optimized using *Fa%* at $Do > 1$ (cf. Eq. (1) can be approximated as $Fa \approx Pn/Do = Pn \times S_{dissolv} \times V_{GI}/Dose$.). The optimized V_{GI} was 130 mL. This value is within the previously reported range of 50–250 mL. In Fig. 1, the effect of V_{GI} on *Fa%* estimation for these four SL-E drugs is shown. It should be noted that the uncertainty in the solubility values was considered to be negligible as these compounds are undissociable at a neutral pH and hydrophilic ($\log P_{oct} < 0.5$), and therefore, their solubility values are insensitive to pH and bile micelle concentration which has some uncertainty in the literature values (Mithani et al., 1996). Given the variability in *Fa%*, it might be difficult to strictly conclude the V_{GI} value among 50–250 mL, though the probability that ca. 130 mL being the mean value would be high. 50–250 mL corresponds to ca. 3–12% of the full volume of the intestinal tube (cf., 1.5 cm radius and 300 cm length (ca. 2000 mL)). This is in good agreement with the intestinal tube being more like a deflated fire hose, rather than a perfect cylindrical tube fully filled with the fluid. Previously, the degree of flatness (DF) was estimated to be 1.7 from the human P_{eff}–*Fa%* relationship of permeability limited cases (Fagerholm and Lennernaes, 1995; Sugano, 2009a). This DF value corresponds to an ellipse with the aspect ratio of ca. 1:5, further supporting the deflated tube shape. On the other hand, together

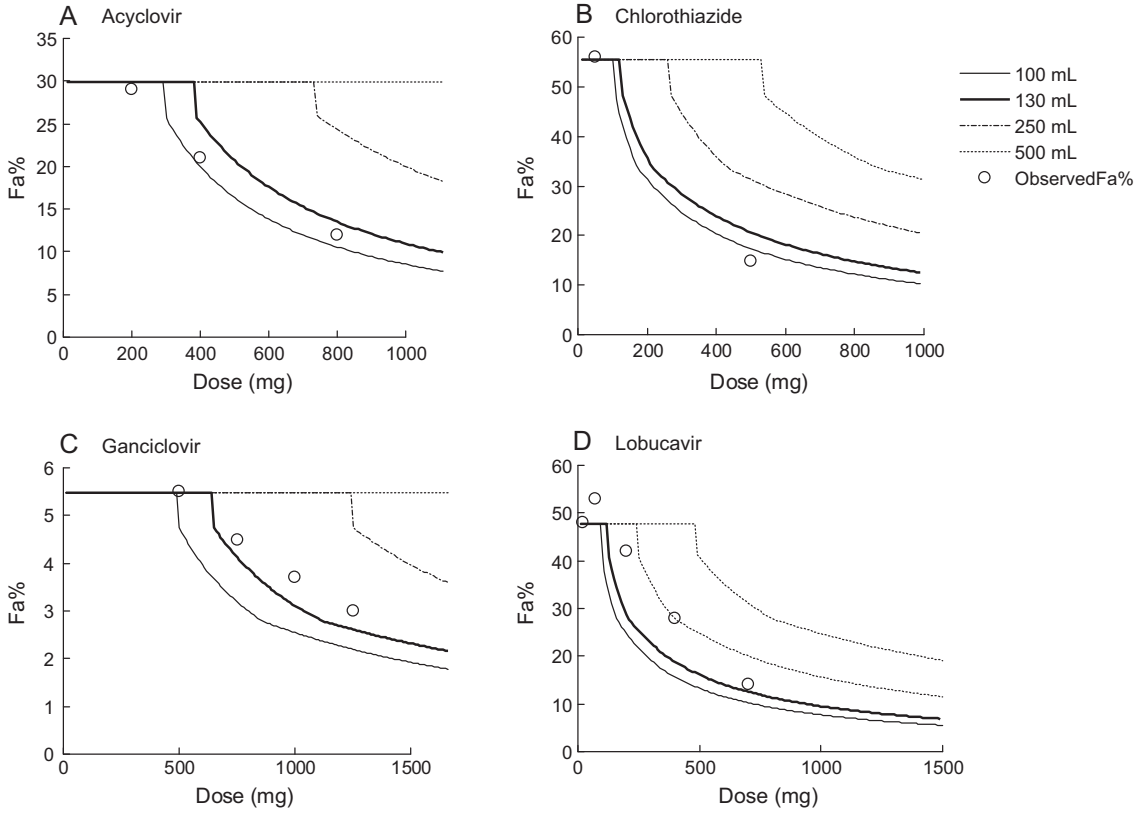

Fig. 1. Effect of the intestinal fluid volume on the dose dependency of solubility–epithelial membrane permeability limited cases.

with the previously reported V_{GI} values, it can be concluded that >500 mL (>25% of the full volume) is out of the realistic range.

h_{UWL} was then optimized using the cases where the PDE is negligible, i.e., *Dose* < 5 mg/kg and mean particle diameter (d50) > 10 μm (cilostazol, irbesartan, phenytion and spironolacton) (Sugano, 2010c). The optimized h_{UWL} value was 332 μm. This value is very close to the experimentally estimated value by Lennernas and coworkers (Lennernaes, 2007) and the computationally simulated value by Wang et al. (2010). C_{pd} and R_{mucus} were then simultaneously optimized using all set of *Fa%* data. C_{pd} and R_{mucus} were 2.2 and 2.9 μm, respectively. This R_{mucus} value is in the similar dimension to the reported pore radius of the mucus meshes (at least >0.5 μm) (Cone, 2009).

The overall correlation between predicted and observed *Fa%* is shown in Fig. 2. In most cases (ca. 80%), the prediction error was within 2 fold (the average error was 1.6 fold). The method of the present study appropriately predicted both the dose dependency, particle size effect (via dissolution rate or PDE), and the food effect for low solubility compounds.

Previously, for PL cases (=low permeability/high solubility), the mechanistic approach employed in the GUT framework was found to appropriately predict *Fa%* and P_{eff} for structurally diverse drugs, using various levels of input data such as $\log P_{oct}$/pK_a/MW (Obata et al., 2005; Sugano, 2009g; Sugano et al., 2006), PAMPA (Sugano et al., 2002, 2003), and Caco-2 (Saitoh et al., 2004). Similar mechanistic approaches to predict permeability were also used by the other investigators to predict *Fa%* and P_{eff} (Avdeef and Tam, 2010; Reynolds et al., 2009), corroborating the appropriateness of the mechanistic approach employed by the GUT framework for the PL cases. In addition, predictability of the GUT framework for *Fa%* of low solubility free bases with the low pH stomach was recently investigated (Sugano, 2010b). Together with the results of this study, the overall *Fa%* predictability of the GUT framework for a range of PL, DRL, SL-E and SL-U was found to be sufficient for the use in drug discovery and early drug development, except for salt form cases which would require nucleation mechanism to be taken into the GUT framework (Sugano, 2009c,e).

However, for a drug development purpose (such as a virtual bioequivalence study), much better quantitative prediction is required. Therefore, further refinements of the drug and physiological parameters are required as well as the model equation refinements. Several reasons can be raised for the remaining error. In this study, the solubility of a drug in the artificial intestinal fluids was assumed to be similar to that in the real intestinal fluid. How-

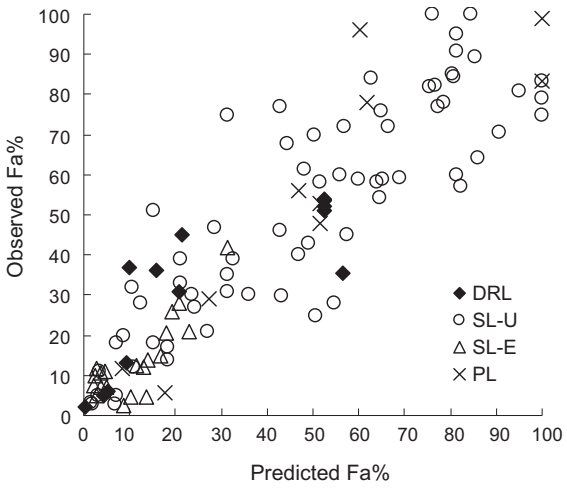

Fig. 2. Overall predictability of the GUT framework for low solubility compounds. Solubility in biorelevant media, molecular weight, log *P*, pK_a, Caco-2 permeability, dose and particle size were used as the input parameters to predict *Fa%*.

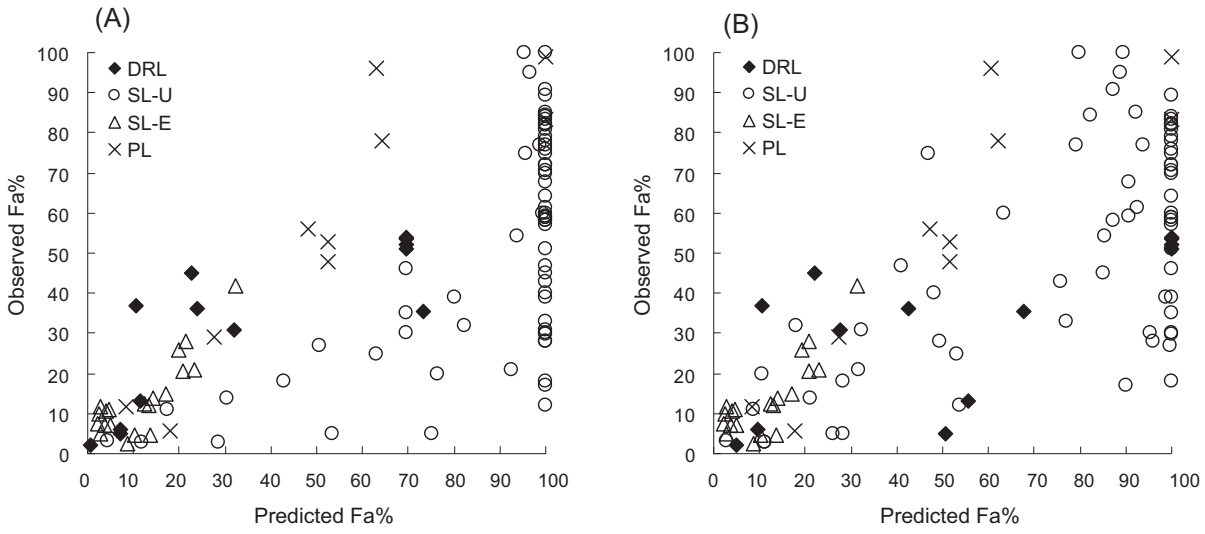

Fig. 3. Effect of UWL and bile micelle diffusion on *Fa%* prediction. (A) UWL ignored case. (B) Bile micelle diffusion ignored case.

ever, these values could have 2 fold or more differences (Clarysse et al., 2009). Even when comparing the real solubility values in the real intestine fluids, a few fold discrepancy was found in the literature, probably depending on the difference of the fluid collection method (Soederlind et al., 2010). An intensive intubation may increase the fluid secretion and decrease the concentration of bile micelles. In addition, the sampling position would also affect the bile concentration. The bile concentration was found to be higher in the jejunum than in the duodenum as the water absorption would concentrate the bile (Dietschy, 1968; Perez de la Cruz Moreno et al., 2006). The drug inclusion into bile micelles was assumed to have little effect on D_{eff}. However, D_{bm} of drug included micelles was found to deviate from that of the D_{bm} of blank micelle ca. average 20% for neutral and acidic compound and average 60% for basic drugs in a case by case manner (Okazaki et al., 2007). The D_{mono} estimation from MW has an estimation error of 20% (Avdeef, 2010). Spherical particle assumption is used to calculate *Dn* (but would be less than two fold error for most cases) (Sugano, 2010a). Further refinement of this estimation scheme will increase the prediction accuracy. However, there is also inherent uncertainty in *Fa%* data estimated from the clinical PK data. No specific reason for the prediction error could be identified after analyzing the correlation between the prediction error and input data.

The permeation resistance from the UWL is often ignored in oral absorption simulation. However, when the permeation resistance from the UWL was ignored, *Fa%* of the SL-U cases were overestimated (Fig. 3A). The UWL determines the upper limit of P_{eff} and should be taken into account in the case of lipophilic compounds ($\log D > 0.5$–2). Even for metoprolol which has been used as a borderline marker permeant of high/low permeability ($P_{eff} = 1.3 \times 10^{-4}$ cm/s) (Lennernaes, 2007), ca. 50% of the permeation resistance was found to be due to the UWL (Avdeef and Tam, 2010). An in vitro membrane permeation study such as Caco-2 can have various UWL thickness values depending on the agitation strength and the apparatus size and shape (Korjamo et al., 2008, 2009). It could coincidentally give an appropriate UWL permeability as a thick UWL of an in vitro system (~1500–3000 μm) could cancel out the lack of villi expansion, resulting in similar P'_{ep}/P_{UWL} ratio. However, this point should not be misapprehended as that the effect of UWL is negligible in $P_{app} - P_{eff}$ extrapolation. The $\log P_{eff} - \log P_{app}$ extrapolation line was validated only for low to medium lipophilicity compounds and not for high lipophilicity compounds (Sun et al., 2002).

The effect of bile micelle diffusion is also often ignored in oral absorption simulation. Fig. 3B shows the effect of bile micelle diffusion on *Fa%* prediction. Bile micelle binding reduces the effective diffusion coefficient of a drug, resulting in a reduction in the dissolution rate and UWL permeability of a drug. Therefore, when bile micelle diffusion was ignored and monomer diffusion was used, *Fa%* of DRL and SL-U cases were overestimated. This result is consistent with the previous findings (Okazaki et al., 2008; Sugano, 2009a,d).

Majority of low solubility drugs ($Do > 1$) used in this study was categorized as SL-U (Table 3), but not DRL. This is reasonable from the view point of the practical drug development. Particle size reduction is usually employed to mitigate dissolution rate limitation when incomplete oral absorption was observed during drug development. The critical particle size which discriminate the DRL and SL can be calculated as follows. The criterion of $1/Dn > Do/Pn$ (for $Do > 1$) can be rearranged to:

$$\frac{1}{Dn} = \frac{r_p^2 \rho}{3 \cdot D_{eff} \cdot S_{dissolv} \cdot T_{si}} > \frac{Do}{Pn} = \frac{Dose}{S_{dissolv} \cdot V_{GI}} \frac{R_{GI}}{2DF \cdot P_{eff} \cdot T_{si}} \quad (15)$$

By rearranging this equation, the critical radius to become dissolution rate limited absorption can be calculated as,

$$r_p > \sqrt{\frac{3D_{eff} \cdot Dose \cdot R_{GI}}{2 \cdot V_{GI} \cdot DF \cdot P_{eff} \cdot \rho}} \quad (16)$$

$S_{dissolv}$ is cancelled out from the both side of Eq. (15) suggesting that the critical particle size dose not depend on the solubility of a drug for $Do > 1$ cases (cf. for neutral drugs, $S_{dissolv} = S_{surface}$). This point can be interpreted as: when the solubility is low, the dissolution rate becomes slow, and at the same time, the ceiling of the dissolved drug concentration (=saturated solubility) becomes low. On the other hand, when the solubility is high, the dissolution rate becomes fast and the ceiling of the dissolved drug concentration also becomes high. Therefore, the tendency to reach the ceiling of saturated solubility (=becoming SL absorption) does not depend on the solubility of a drug for the $Do > 1$ cases, however, does depend on P_{eff}, Dose and particle size (in other words, the tendency to deviate from the sink condition does not depend on $S_{dissolv}$ for the $Do > 1$ cases). The mean particle size can be usually reduced to 10 μm or less. Therefore, according to Eq. (15), even for relatively high P_{eff} cases of 5×10^{-4} cm/s (before applying PDE), when the dose is >20 mg, the oral absorption becomes solubility–permeability limited, but not dissolution rate limited. This is in good agreement with our real-life experience in drug industries that a quantitative

IVIVC is difficult to obtain by using a standard dissolution test for medium to high dose cases of low solubility compounds, whereas it was obtainable for low dose cases such as digoxin (0.5 mg dose).

Considering the particle drifting effect for SL-U cases, particle size reduction could increase the oral absorption even in the case of solubility–permeability limited cases. Therefore, an apparent rank order correlation (but not a quantitative IVIVC) between the dissolution rate and in vivo oral absorption can be a superficial correlation intermediated by the effect of the particle size on both the in vitro dissolution rate and in vivo PDE. For SL-U cases, a dissolution–permeation (D/P) type in vitro method is more appropriate (Kataoka et al., 2003, 2006). For example, the D/P system was found to quantitatively predict the oral absorption of fenofibrate under a non-sink condition (Buch et al., 2009).

In conclusion, by using the GUT framework with in vitro data routinely measured in drug discovery, *Fa*% was predicted with a practically useful accuracy for drug discovery, but not enough accuracy for drug development.

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