Calculation of fraction of dose absorbed: comparison between analytical solution based on one compartment steady state concentration approximation and dynamic seven compartment model

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Abstract

Oral absorption of a drug is modeled by the differential equations for dissolution, permeation and gastrointestinal transit processes. The purpose of the present study was to compare simple approximate analytical solutions with full numerical solutions for the calculation of the fraction of a dose absorbed (F_a). The GI compartment model for numerical integration consisted of 1 stomach, 7 intestine and 1 colon compartments, whereas for analytical solutions a simple one well-stirred compartment was used. Full numerical solutions were obtained by numerically integrating the dissolution, permeation and gastrointestinal transit differential equations. In the numerical integration calculation, the concentration change in the GI tract, particle size reduction, transit of drugs, etc., was dynamically simulated. Precipitation in the GI tract and regional differences of solubility and permeability were not considered. In total, 7056 numerical integrations were performed, sweeping practical drug parameter ranges of solubility (0.001 to 1 mg/mL), diffusion coefficient ($0.1 - 10 \times 10^{-6} \text{ cm}^2/\text{sec}$), dose (1 to 1000 mg), particle diameter (1 to 300 μm) and effective permeability ($0.03 - 10 \times 10^{-4} \text{ cm/sec}$). The analytical solutions investigated were (I) a sequential first order approximation ($F_a = 1 - P_n/(P_n - D_n)\exp(-D_n) + D_n/(P_n - D_n)\exp(-P_n)$, D_n : dissolution number, Do : dose number and P_n : permeation number. D_n , Do and P_n are the dimensionless parameters which represent the dissolution time/GI transit time ratio, the solubility/dose ratio, and the permeation time/GI transit time ratio, respectively), (II) a limiting step approximation (the minimum value of $F_a = 1 - \exp(-P_n)$, $F_a = P_n/Do$ and $F_a = 1 - \exp(-D_n)$) and (III) a steady state approximation for the dissolved drug concentration ($F_a = 1 - \exp(-1/(1/D_n + Do/P_n))$, if $Do < 1$, $Do = 1$). F_a values by (I) and (II) were higher than those by numerical integration for low solubility compounds ($r^2 = 0.80$ and 0.98 , root mean square error (RMSE) = 0.28 and 0.079 , respectively). By applying the steady state approximation, the correlation was improved ($r^2 = 0.99$, RMSE = 0.047). The steady state approximation for the dissolved drug concentration was appropriate for F_a calculation.

Key Words: Solubility, Permeability, Dissolution rate, Fraction of a dose absorbed

Area of Interest: Information and Computing Infrastructure for Drug Design and Toxicology

1. Introduction

Prediction of in vivo oral absorption from in vitro solubility and permeability data is important in drug discovery and development [1][2][3][4][5]. Theoretical frameworks to calculate oral absorption have been extensively investigated over the last two decades [6][7][8][9][10][11][12]. Oral absorption is basically determined by dissolution, precipitation, permeation and gastrointestinal (GI) transit of a drug [1]. Since these processes are described in a form of a differential equation, these differential equations have to be simultaneously solved to obtain a calculation result, e.g., the fraction of a dose absorbed (Fa). Computational numerical integration is widely used to solve the differential equations.

To express the GI transit of drug particles and dissolved drug molecules, several multi-compartment models have been introduced [11][13][14][15], e.g., the advanced compartmental absorption transit model (ACAT model) [11], the gastrointestinal transit absorption model (GITA model) [13], and the advanced dissolution absorption metabolism model (ADAM model) [14]. These models have one stomach compartment, seven small intestine compartments and one colon compartment (S1I7C1 model) [11][13]. Other compartment models have also been used for oral absorption simulation, such as one stomach, one small intestine and one colon compartment model (S1I1C1 model) [7][8][16]. There are several commercially available programs which employ GI compartment models, such as SimCYP, GastroPlus, IntelliPharm, etc. These programs numerically solve the differential equations of dissolution and permeation together with that of the GI transit. By using numerical integration, the change of the drug concentration in the GI fluid, the transit of drug particles and dissolved drugs are dynamically and quantitatively simulated.

However, an analytical solution is still valuable. An analytical solution can enhance understanding of oral absorption processes as it explicitly describes the impact of each parameter. In addition, due to its computational expense, numerical integration is not suitable for a large batch of compounds. Recently, a large amount of data are produced by routine high throughput screening for solubility and permeability [2][17][18][19].

The limiting steps of oral absorption can be categorized into three types: permeability, dissolution rate and solubility limited [2][10][20]. Analytical solutions of Fa for these limiting cases were reported in late 1980's and early 1990's [8][9][15]. Recently, by applying a steady state approximation for the dissolved drug concentration in the GI fluid, approximate analytical solution for low solubility compounds was obtained, which could cover all three limiting cases and intermediate cases [1]. However, the validity of this approximation has not been fully investigated. The purpose of the present study was to compare the analytical solutions and the full numerical solution of a dynamic S1I7C1 model.

2. Theory

The equations used in the present study were previously described in detail [1][5][21][22], and therefore, are only briefly described in this article. In the present study, only undissociable drugs were considered. In addition, the effective concentrations for dissolution and permeation are assumed to be the same [1][2].

2.1 Differential equations

2.1.1 Dissolution process

Dissolution of drug particles is described by the Nernst Brunner equation as,

$$\begin{aligned} \frac{dX_{API,ij}}{dt} &= -\frac{dX_{dissolv,k}}{dt} = -SA_{API,ij} \cdot \frac{D_{eff}}{h_{pUWL,ij}} \cdot (S_{dissolv} - C_{dissolv,k}) \\ &= -\frac{3D_{eff} \cdot f_{ij} \cdot Dose^{1/3} X_{API,ij}^{2/3}}{\rho \cdot h_{pUWL,ij} \cdot r_{p,ij,t=0}} \cdot (S_{dissolv} - C_{dissolv,k}) \end{aligned} \quad 1$$

where $X_{API,ij}$ is the amount of a drug (weight or mol) in a particle size bin i , and a virtual particle bin j within each particle size bin, $X_{dissolv,k}$ is the dissolved drug amount at a GI position k , $SA_{API,ij}$ is the total solid surface area of a particle bin, $h_{pUWL,ij}$ is the effective diffusion resistance of the unstirred water layer on the particle surface, D_{eff} is the effective diffusion coefficient, f_{ij} is the fraction of a dose ($Dose$), $S_{dissolv}$ is the solubility of a drug, $C_{dissolv,k}$ is the concentration of a dissolved drug in the GI fluid at a GI position k ($C_{dissolv,k} = X_{dissolv,k} / V_{GI,k}$), $r_{p,ij}$ is the particle radius, ρ is the true density of a drug (set to 1.2 g/cm³), and $V_{GI,k}$ is the volume of the GI fluid. The particle bins are introduced to represent the particle size distribution and GI transit of drug particles. The surface area of a particle group ij is calculated as,

$$N_{API,ij} = \frac{f_{ij} \cdot Dose}{\frac{4}{3} \pi \cdot r_{p,ij,t=0}^3 \cdot \rho} \quad 2$$

$$\begin{aligned} SA_{API,ij} &= N_{API,ij} \cdot 4\pi r_{p,ij}^2 = \frac{f_{ij} \cdot Dose}{\frac{4}{3} \pi \cdot r_{p,ij,t=0}^3 \cdot \rho} \cdot 4\pi r_{p,ij}^2 = \frac{3f_{ij} \cdot Dose}{r_{p,ij,t=0} \cdot \rho} \cdot \left(\frac{r_{p,ij}}{r_{p,ij,t=0}} \right)^2 \\ &= \frac{3f_{ij} \cdot Dose}{r_{p,ij,t=0} \cdot \rho} \cdot \left(\left(\frac{X_{API,ij}}{Dose} \right)^{1/3} \right)^2 = \frac{3f_{ij} \cdot Dose^{1/3} \cdot X_{API,ij}^{2/3}}{r_{p,ij,t=0} \cdot \rho} \end{aligned} \quad 3$$

$$r_{p,ij} = \left(\frac{X_{API,ij}}{N_{API,ij}} \cdot \frac{1}{\rho} \cdot \frac{3}{4\pi} \right)^{1/3} \quad 4$$

where $N_{API,ij}$ is the number of drug particles in the ij th particle bin, f_{ij} is the fraction of a dose ($Dose$) in the particle bin ij , and $r_{p,ij,t=0}$ is the initial particle radius ($t = 0$).

2.1.2 Permeation process

Intestinal membrane permeation of dissolved drug molecules is described as,

$$\frac{dX_{abs,k}}{dt} = DF \cdot \frac{2}{R_{GI}} \cdot P_{eff} \cdot V_{GI,k} \cdot C_{dissolv,k} = k_{abs} \cdot X_{dissolv,k} \quad 5$$

where X_{abs} is the absorbed amount, DF is the degree of flatness of the intestinal tube representing the deviation from the cylindrical tube, R_{GI} is the GI tract radius, and P_{eff} is effective intestinal membrane permeability. $DF = 1.7$, $R_{GI} = 1.5$ cm, $V_{GI} = 250$ mL were used in this study (ref. [22] and references therein).

2.1.3 GI transit process

GI transit was described by first order kinetics as,

$$\frac{dN_{API,GI,k}}{dt} = -K_{t,k} \cdot N_{API,GI,k} \quad 6$$

$$\frac{dX_{dissolv,k}}{dt} = -K_{t,k} \cdot X_{dissolv,k} \quad 7$$

where $N_{API,GI,k}$ is the number of API particle bins in a GI position k , and $K_{t,k}$ is the first order transit rate constant (= compartment number/ mean transit time (T_{si})). T_{si} was set to 3.5 hours [23].

2.1.4 Mass balance of dissolved drug in a compartment

The mass balance of dissolved drug in a compartment k is described as,

$$\frac{dX_{dissolv,k}}{dt} = (K_{t,k-1} \cdot X_{dissolv,k-1} - K_{t,k} \cdot X_{dissolv,k}) + \left(\sum_{\substack{i,j \\ \text{if } GIP_{ij}=k}} -\frac{dX_{API,ij}}{dt} \right) - \frac{dX_{abs,k}}{dt} \quad 8$$

where GIP_{ij} represents the GI position of a particle bin ij at time t . The first parenthesis represents the flow-in of dissolved drug from the previous compartment and flow-out into the next compartment. The second parenthesis represents the dissolution of drug particles in the GI compartment. The last term represents absorption into the body.

2.2. Numerical integration of dynamic S1I7C1 model

Fa can be obtained by solving Eqs.1-8. For dynamic numerical integration, the GI tract was represented as one stomach compartment, seven small intestine compartments and one colon compartment (S1I7C1 model). Numerical integration was performed as previously reported to calculate Fa (Fa_{NI}) [1][21][22]. Particle size distribution, movement of particles, particle size reduction by dissolution, and dynamic change of concentration in the GI fluid are fully simulated. $h_{pUWL,ij}$ was calculated from $r_{p,ij}$ and ρ by the fluid dynamic model as previously reported [24]. Drug

particles were assumed to sediment when the terminal velocity was larger than 0.0023 m/sec which corresponds to 50 rpm in the USP 2 paddle method. Asymptotic diffusion was assumed for the sediment particles (i.e., $h_{pUWL,ij} = r_{p,ij}$). The particle size bin number (i) and virtual particle bin number (j) were set to 20 and 100, respectively. Log normal distribution with s.d. of 0.3 log unit was assumed for particle size distribution. The forth Runge-Kutta method was used with 1 min interval. The duration of numerical integration was set to 8 hours to cover the transit time through the small intestine. The program was written in Excel Visual Basic Application.

2.3. Approximate analytical solutions

Since Eqs.1-8 are partial derivative equations, it would be difficult to have an exact analytical solution for Fa . Therefore, approximate analytical solutions of Fa were investigated. By approximating $Dose^{1/3} \cdot X_{API}^{2/3} \approx X_{API}$ and $h_{pUWL,ij} \approx r_{p,ij,t=0}$, Eqs.9-11 can be derived from Eqs.1, 5 and 8 as:

$$\frac{dX_{API}}{dt} \approx -\frac{3D_{eff} \cdot f_{ij} \cdot X_{API}}{\rho \cdot r_{p,ij,t=0}^2} \cdot (S_{dissolv} - C_{dissolv,k}) = -k_{disso} \cdot X_{API} \cdot \left(1 - \frac{C_{dissolv}}{S}\right) \quad 9$$

$$\frac{dX_{dissolv}}{dt} = k_{disso} \cdot X_{API} \cdot \left(1 - \frac{C_{dissolv}}{S}\right) - k_{abs} \cdot X_{dissolv} \quad 10$$

$$\frac{dX_{abs}}{dt} = k_{abs} \cdot X_{dissolv} \quad 11$$

The analytical solutions were obtained by integrating Eqs.9-11 for the mean intestinal transit time (T_{si}). To avoid difficulties from the GI transit equations (Eq.6 and 7), the small intestine was approximated as one well-stirred compartment equipped with a membrane without flow-in and flow-out of the fluid (corresponding to a dissolution test beaker equipped with a membrane (such as the dissolution - permeation system [25][26])). At time = 0, the drug dosage was directly put into the compartment at once. The dissolution and permeation then occur in the compartment. At time = T_{si} , all drug particles and dissolved drug exit from the compartment at once and the oral absorption terminates (S011C0 model). Even though this model is simple, this model was successfully used previously [20][27].

To simplify the following equations, the permeation number (Pn), the dose number (Do), and the dissolution number (Dn) were first defined as previously reported by Oh et al. [9]:

$$Pn = \left(\frac{2DF}{R_{GI}} \cdot P_{eff}\right) \cdot T_{si} = k_{abs} \cdot T_{si} \quad 12$$

$$Do = \frac{Dose}{S_{dissolv} \times V_{GI}} \quad 13$$

$$Dn = \left(\frac{3 \cdot D_{eff} \cdot S_{dissolv}}{\rho} \left(\sum_i \frac{f_i}{r_{p,i,t=0}^2}\right)\right) \cdot T_{si} = k_{disso} \cdot T_{si} \quad 14$$

The definition of Pn in this article is different from the original definition of absorption number (An) by a factor of 2 ($An = DF \cdot P_{eff} \cdot T_{si} / R_{GI}$). However, to simplify the following discussions and avoid confusion, Pn is used in this article. The number of 2 is originated from the formula of circumference ($2\pi r$) and it might be usual to include it into a lump dimensionless parameter. Dn was modified from the previous definition, taking into consideration the particle size distribution.

2.3.1 Sequential first order approximation

When $C_{dissolv}/S_{dissolv} \ll 1$, oral absorption becomes a sequential first order process and an analytical solution for Fa (Fa_{sfo}) is:

$$\begin{aligned}
 Fa_{sfo} &= 1 - \frac{k_{abs}}{k_{abs} - k_{diss}} \exp(-k_{diss} \cdot T_{si}) + \frac{k_{diss}}{k_{abs} - k_{diss}} \exp(-k_{abs} T_{si}) \\
 &= 1 - \frac{Pn}{Pn - Dn} \exp(-Dn) + \frac{Dn}{Pn - Dn} \exp(-Pn) \quad C_{dissolv}/S \ll 1.
 \end{aligned} \tag{15}$$

2.3.2 Limiting cases approximation

Considering the three limiting cases of each permeability, solubility and dissolution rate limited absorption, and taking the minimum value, we can obtain an analytical solution for Fa ($Fa_{min.limit}$). The analytical solutions of Fa for each limiting case are,

$$Fa_{Pn} = 1 - \exp(-k_{abs} \cdot T_{si}) = 1 - \exp(-Pn) \tag{16}$$

$$Fa_{Pn/Do} = k_{abs} \cdot T_{si} \cdot \frac{S \cdot V_{GI}}{Dose} = \frac{Pn}{Do} \tag{17}$$

$$Fa_{Dn} = 1 - \exp(-k_{disso} \cdot T_{si}) = 1 - \exp(-Dn) \tag{18}$$

Eq.16 was obtained by integrating Eq.11 from time zero to T_{si} , assuming immediate complete dissolution ($X_{dissolv}(t = 0) = Dose$). Eq.16 has been widely used to correlate the membrane permeability and Fa . Similarly, Eq.18 was obtained by integrating Eq.9, assuming immediate complete permeation after dissolution (therefore, the intestine is in the sink condition ($C_{dissolv} \approx 0$)). Eq.17 is related to the concept of the maximum absorbable dose ($MAD = k_a \cdot S_{dissolv} \cdot V_{GI} \cdot T_{si}$) [28], in which $C_{dissolv}$ was assumed to be maintained as the saturated solubility ($S_{dissolv}$)(cf. Eq. 11 becomes $dX_{abs}/dt = k_a \cdot S_{dissolv} \cdot V_{GI}$. Therefore, $X_{abs} = k_a \cdot S_{dissolv} \cdot V_{GI} \cdot T_{si}$). Eq.16 and 17 can also be obtained by the plug flow model [9]. By taking the minimum value of Eq.16-8, we obtain an estimate of Fa ($Fa_{min.limit}$),

$$Fa_{min.limit} = Minimum(Fa_{Pn}, Fa_{Pn/Do}, Fa_{Dn}) \tag{19}$$

2.3.3 Steady state approximation for dissolved drug concentration

By applying the steady state approximation for the dissolved drug concentration (so that $C_{dissolv}$ becomes a steady value (C_{ss}) when the dissolution and permeation rates balance) [1][5], we obtain,

$$\frac{dX_{dissolv}}{dt} = k_{disso} \cdot X_{API} \cdot \left(1 - \frac{C_{ss}}{S_{dissolv}}\right) - k_{abs} \cdot C_{ss} \cdot V_{GI} = 0 \tag{20}$$

By opening Eq.20 for C_{ss} at the initial time (so that $\sum X_{API,i} = Dose$), normalizing by $S_{dissolv}$, and inserting to Eq.18, Fa with a steady state concentration approximation (Fa_{ss}) can be calculated as:

$$Fa_{ss} = 1 - \exp\left(-\frac{1}{\frac{1}{k_{diss}} + \frac{Do}{k_{abs}}} \cdot T_{si}\right) = 1 - \exp\left(-\frac{1}{\frac{1}{Dn} + \frac{Do}{Pn}}\right) \quad \text{If } Do < 1, Do = 1. \quad 21$$

The initial saturation number (Sn_{ini}) which indicates the degree of sink/non-sink conditions in the intestinal fluid can also be calculated as [1],

$$Sn_{ini} = \frac{C_{ss}}{S_{dissolv}} = \frac{1}{1 + \frac{k_{abs}}{Do \cdot k_{diss}}} = \frac{1}{1 + \frac{Pn}{Do \cdot Dn}} \quad Do > 1. \quad 22$$

When Sn_{ini} is close to 1, the drug concentration in the intestinal fluid is close to the saturated solubility, whereas when Sn_{ini} is close to zero, it is in the sink condition. Fa_{ss} smoothly connects to the three limiting cases of Fa_{Pn} , $Fa_{Pn/Do}$ and Fa_{Dn} (for $Fa_{Pn/Do}$, cf. $x < 0.7$, $1 - \exp(x) \approx x$). Therefore, Fa_{ss} includes the three limiting cases.

3. Results

The S1I7C1 system is widely used for the simulation of oral absorption. The ACAT (GastroPlus), GITA[13][29], and ADAM (SimCYP) models all employ the S1I7C1 system. Therefore, the S1I7C1 system was selected as a subject of comparison. The analytical solutions investigated in the present study correspond to one well-stirred compartment model equipped with a membrane without flow-in and flow-out of the fluid (S0I1C0 system).

The drug parameters used for Fa calculation are summarized in Table 1. Five drug parameters which determine Fa were swept to cover the practical parameter range. A wide D_{eff} range (down to $0.1 \times 10^{-6} \text{ cm}^2/\text{sec}$) was employed to cover the diffusion of bile micelle dissolved drug molecules [21]. In total, 7056 numerical integrations were performed to obtain Fa values by the dynamic S1I7C1 system. Fa values calculated by the analytical solutions (Fa_{sfo} , $Fa_{limit.min}$ and Fa_{ss}) were then compared with those by the numerical solution (Table 2, Figure. 1 - 4).

Table 1. Drug parameters used for Fa calculation

Drug parameter	Values
$Dose$ (mg)	1, 3, 10, 30, 100, 300, 1000
P_{eff} ($\times 10^{-4} \text{ cm/sec}$)	0.03, 0.1, 0.3, 1, 3, 10
D_{eff} ($\times 10^{-6} \text{ cm}^2/\text{sec}$)	0.1, 0.3, 1, 3, 10
$S_{dissolv}$ (mg/mL)	0.001, 0.003, 0.01, 0.03, 0.1, 1
d_p ($= 2r_p$) (μm)	1, 3, 10, 30, 100, 300

Table 2. Correlation coefficient (r^2) and root mean square error (RMSE)

BCS	Compound number	r^2				RMSE			
		Fa_{sfo}	$Fa_{limit,min}$	Fa_{SS}	Fa_{SScorr}	Fa_{sfo}	$Fa_{limit,min}$	Fa_{SS}	Fa_{SScorr}
1	720	0.981	0.977	0.983	0.992	0.071	0.078	0.066	0.058
2	1632	0.702	0.981	0.989	0.992	0.393	0.094	0.059	0.049
3	1440	0.994	0.968	0.990	0.996	0.038	0.091	0.050	0.030
4	3264	0.667	0.971	0.985	0.998	0.291	0.065	0.032	0.012
Total	7056	0.803	0.982	0.992	0.995	0.275	0.079	0.047	0.034

Figure 1. Fa calculated by sequential first order approximation (Fa_{sfo}) vs by numerical integration of the S1I7C1 system (Fa_{NI}).

Figure 2. Fa calculated as the minimum value of limiting cases ($Fa_{min,limit}$) vs by numerical integration of the S1I7C1 system (Fa_{NI}).

Figure 3. Fa calculated by the analytical solution with a steady state dissolved drug concentration (Fa_{SS}) vs by numerical integration of the S1I7C1 system (Fa_{NI}).

Figure 4. Fa calculated by corrected steady state approximation ($Fa_{SS,corr}$) vs by numerical integration of the S1I7C1 system (Fa_{NI}).

Figure 5. F_a analytical solutions for permeation limited absorption, S0I1C0 (solid line) and S1I7C1 systems (dotted line).

The sequential first order approximation (Eq.15, $F_{a_{sfo}}$) resulted in overestimation in the case of low solubility compounds (biopharmaceutical classification system (BCS) class II and IV compounds [30])(Figure 1, Table 2), due to neglecting the effect of solubility limitation in the GI fluid. In the case of high solubility compounds (BCS I and III), the correlation was appropriate. This is not surprising since the analytical solutions of permeation limited cases for the S1I7C1 system (right hand side of Eq.23) and the S0I1C0 system (left hand side of Eq.23) are almost identical (Figure. 5)[15].

$$1 - \exp(-Pn) \approx 1 - \left(1 + \frac{Pn}{7}\right)^{-7} \quad 23$$

Even in the case of BCS I, some compounds showed incomplete absorption due to a slow dissolution rate. A large particle size or a small diffusion coefficient can cause slow dissolution. Since the permeability is high for BCS I compounds, oral absorption becomes dissolution rate limited and the first order approximation was appropriate.

The analytical solution taking the minimum value of the three limiting cases (Eq.19, $F_{a_{min.limit}}$) was then compared with numerical integration (Figure 2). $F_{a_{min.limit}}$ roughly correlated with $F_{a_{NI}}$. However, $F_{a_{min.limit}}$ tended to overestimate F_a . This result confirmed the previous findings in a small number of cases [1][5]. This overestimation is due to over and under estimation of the GI concentration in $F_{a_{Pn/Do}}$ and $F_{a_{Dn}}$ calculations, respectively. In many cases, oral absorption could be an intermediate between the solubility and dissolution rate limited cases.

By applying a steady state approximation for the dissolved drug concentration ($C_{dissolv}$) (Eq.21, $F_{a_{SS}}$), the correlation between the analytical solution and numerical integration was improved (Figure 3), especially for BCS II and IV. It is interesting that one simple equation in the form of Eq. 21 can cover a wide range of compound conditions, even though extensive simplifications were applied to derive this analytical solution (cf. 2.3).

However, some deviations still remained. Three reasons were identified: (A) $C_{dissolv}$ did not reach the steady state during the GI transit (Figure 6A), (B) the initial steady state concentration was not maintained due to the dissolution rate being reduced (particle size reduction occurred as particles dissolved) (Figure 6B) and (C) the steady state concentration was maintained longer than T_{si} due to the particles remaining in the GI tract after T_{si} (Figure 6C) [22]. (A) and (B) are due to a deviation from the steady state concentration approximation, whereas (C) is caused by neglecting the dispersion of drug particles along the GI tract which is represented in the S1I7C1 model [1][22][23] (drug particles gradually exit from the small intestine, but not at once as assumed for the analytical solutions (cf. 2.3)). (A) and (B) resulted in $F_{a_{SS}} > F_{a_{NI}}$, whereas (C) resulted in $F_{a_{SS}} < F_{a_{NI}}$.

Figure 6. Typical case examples showing a deviation from the steady state concentration and one compartment approximations. (A) $C_{dissolv}$ did not reach the steady state concentration during the GI transit, (B) the initial steady state concentration was not maintained, and (C) the steady state duration was longer than T_{si} . Drug parameters used for Fa calculation were indicated in the figures. The lines in the figures correspond to each small intestinal compartment (From left to right, compartment 1 to 7, proximal to distal, respectively).

In the case of (A), $C_{dissolv} < S_{dissolv}$. Therefore, the sequential first order kinetic model is appropriate. Appropriate Fa can be obtained by replacing Fa_{SS} with Fa_{sfo} when $Fa_{sfo} \times 1.15 < Fa_{SS}$. The coefficient of 1.15 was introduced as a margin to ensure a definite sink condition. This treatment improved the correlation at the $Fa < 0.2$ range.

To correct (B) and (C), the steady state reduction correction factor (CF_{SSR}) and the extended steady state duration number (Tn_{exss}) can be introduced to Eq.21 as:

$$Fa_{ss,corr} = 1 - \exp\left(-\frac{1}{\frac{1}{Dn} + \frac{Do}{Pn}} \cdot CF_{SSR} \cdot Tn_{exss}\right) \quad \text{If } Do < 1, Do = 1. \quad 24$$

CF_{SSR} was calculated considering the saturation number at time T_{si} (Sn_{Tsi}). Fa is first calculated without any correction by Eq.21 (Fa'). By using Fa' to consider the reduction of Do and Dn during the oral absorption processes (i.e., replacing Do and Dn in Eq. 22 with $Do \cdot (1 - Fa')$ and $Dn \cdot (1 - Fa') - 2/3$), and normalizing by Sn_{ini} , the steady state reduction number (SRn) can be obtained as (cf. $r_p/r_{p,t=0} \approx (1 - Fa')^{1/3}$, neglecting $X_{dissolv}$ at time T_{si}),

$$SRn = \frac{Sn_{Tsi}}{Sn_{ini}} = \frac{1}{Sn_{ini} \left(1 + \frac{Pn}{Do \cdot Dn \cdot (1 - Fa')^{1/3}}\right)} \quad 25$$

The mean and standard distribution of particle size was assumed to remain the same [2][6]. CF_{SSR} is then calculated by taking the average as:

$$CF_{SSR} = \frac{1}{2}(Sn_{ini} + Sn_{Tsi}) = \frac{1}{2} Sn_{ini} (1 + SRn) \quad 26$$

CF_{SSR} corrects the decline of drug concentration from an initial steady state concentration. CF_{SSR} was found to be in the range of 0.54 - 1.0.

Tn_{exss} is determined by the amount of drug particles remaining in the GI tract to maintain a steady state concentration. The portion of a drug amount exited from the GI tract until the time t ($EXT(t)$) can be expressed by the S117C1 model or a sigmoid curve as [15][23],

$$EXT(t) = 1 - \exp(-K_t \cdot t) \left(\sum_{n=1}^7 \frac{(K_t \cdot t)^{n-1}}{(n-1)!} \right) \approx \frac{1}{1 + \exp(-k_t \cdot (t - T_{si}))} \quad 27$$

Figure 7. Colon exited fraction expressed by the sigmoidal curve (solid line) and the S1I7C1 systems (dotted line). For the S1I7C1 system, $K_t = 7/T_{si} = 2$ (hour^{-1}) and for the sigmoid curve, $k_t = 1.31$ (hour^{-1}).

Figure 7 shows that the analytical solutions of the colon exited fraction by the S1I7C1 model (Eq.27 middle part) and a sigmoid curve (Eq.27 right hand side, $k_t = 1.31 \text{ hour}^{-1}$). Using $EXT(t)$ and approximation of $Fa \ll 1$, the saturation number at T_{exss} can be calculated as:

$$Sn_{T_{exss}} = \frac{1}{1 + \frac{An}{Do \cdot (1 - EXT(T_{exss})) \cdot Dn}} \quad 28$$

$Do(1 - EXT(t))$ is the dose number at time t taking into account the exit of drug particles from the colon. When $Sn_{T_{exss}}/Sn_{ini} = 1/2$, it can be assumed that the drug amount in the GI tract becomes less than the amount which can maintain the steady state concentration. By using a sigmoidal curve for $EXT(t)$, rearranging $Sn_{T_{exss}}/Sn_{ini} = 1/2$ and normalizing by T_{si} , we obtain Tn_{exss} :

$$Tn_{exss} = \frac{T_{exss}}{T_{si}} = 1 - \frac{1}{k_t \cdot T_{si}} \ln \left(\frac{1}{1 + \frac{DoDn}{An}} \right) \quad Do \cdot (1 - EXT(T_{exss})) > 1 \quad 29$$

The precondition of this equation is that $Do(1 - EXT(t))$ is larger than 1. The time when the drug amount remaining in the GI tract gives $Do(1 - EXT(t)) = 1$ (T_{DOI}) can be calculated by rearranging $Do(1 - EXT(T_{DOI})) = 1$ and normalizing with T_{si} as:

$$Tn_{DoI} = \frac{T_{DoI}}{T_{si}} = 1 - \frac{1}{k_t \cdot T_{si}} \ln \left(\frac{1}{1 - \frac{1}{Do}} - 1 \right) \quad 30$$

When $T_{DoI} > Tn_{exss}$, Tn_{exss} is replaced with T_{DoI} . Tn_{exss} was found to be in the range of 1.0-2.8. By applying CF_{SSR} and Tn_{exss} , the correlation was improved (Figure 4, Table 2). The remaining deviation may be due to the approximations for the correction factors and the dispersion of drug particles and dissolved drug molecules in the GI tract which are represented by the S1I7C1 model, but not by the S0I1C0 model.

4. Discussion

The analytical solutions investigated in this study are applicable for undissociable compounds and the free form of weak acids with low intrinsic solubility. In the cases of weak acids and bases with high intrinsic solubility, the solid surface solubility decreases due to the self-buffering effect by the dissolving drug [2][31][32]. This factor can be represented by using the solid surface solubility ($S_{surface}$) for Dn and the equilibrium solubility in the bulk media (S_{bulk}) for Do [2]. Several theoretical schemes for $S_{surface}$ calculation were reported [31][33][34][35][36]. In the case of weak bases, dissolution in the stomach and precipitation in the intestine have to be taken into account. In the case of salts, an increase of $S_{surface}$ (resulting in faster dissolution) and the supersaturation/nucleation phenomenon (this could result in higher $C_{dissolv}$ during GI transit time) have to be taken into account [1][2][37]. Due to neglecting supersaturation, the analytical solutions investigated in this study correspond to a minimum Fa estimation for weak bases and salts. It would be worth noting that, even though nucleation can be taken into account by a dynamic model [1][37], it is currently difficult to obtain appropriate parameters for nucleation in early drug discovery.

Numerical integration is becoming more easily accessible due to the improvement of computational speed. Numerical integration would be more accurate than the analytical solutions, since it can simulate the dynamic change of the concentration. The differential equations of oral absorption can be simultaneously solved with pharmacokinetic models, such as one compartment, two compartment and physiologically based pharmacokinetic models. We can obtain a concentration - time profile in the intestinal fluid, plasma and other organs. For detailed and accurate simulation, numerical integration is necessary.

However, this may not mean that an exploration of an analytical solution has lost its value. One advantage of an analytical solution is that it can enhance understandability. Even though convenient computational packages are routinely used to solve the differential equations, the analytical solution (and the process to derive it) remains important to understand the essence of oral absorption. Recent improvements in graphical expression can help to enhance the understandability. However, clarity, transparency, simplicity and understandability of an analytical solution would remain valuable [38]. All calculation steps are easily traceable. The understandability is often overlooked in computational approaches for drug research, but is important to appropriately drive a drug research project [12][39]. Fa_{SS} equation (Eq.21) explicitly represents the relationship between solubility, the dissolution rate and permeability.

A calculation by analytical solution is significantly faster than numerical integration. The calculations for 7056 compounds finished in less than 1 second by analytical solution, compared to

ca. 2 days by numerical integration. Even though the calculation speed of numerical integration can be increased by using a faster computer setting and/or a language (Excel VBA is the slowest amongst the computational languages), analytical solution would be quicker and easier to use. Parameter optimization is one application where an analytical solution can offer a benefit, since it often requires a number of iterations of simulations. A large number of calculations would also be required for a database calculation. Currently, more than one million compounds are registered in an in-house compound database.

Considering the balance of simplicity and accuracy, Eq.21 would be the most convenient and useful equation for Fa calculation. $Fa_{min.limt}$ can be used to categorize the oral absorption limiting step which mainly determines Fa , i.e., permeability, the dissolution rate or solubility. Sn_{ini} and Tn_{exss} can be useful key parameters which characterize the extent and duration of saturated concentration in the GI tract.

There is an opinion that dissolution rate limited absorption is not important since Fa is usually solubility limited for a low solubility compound (therefore, Eq.17 is enough. Fa calculations for dissolution rate limited and intermediate cases are not important.). It might be true for marketed drugs since the dissolution rate limitation might have been removed by a milling process before the drug product was put on the market if it had been observed during the drug development stage. Actually, a simulation for particle size dependency is often required in drug discovery and development.

5.Conclousion

In conclusion, for a wide range of compounds, Fa analytical solution based on a steady state concentration approximation was found to give an Fa value similar to that calculated by the full dynamic numerical integration. The difference between Fa_{SS} and Fa_{NI} was small enough for practical estimation of Fa in drug discovery and development. The calculation process is much simpler than numerical integration and even “back of the envelope calculation” is possible. The key dimensionless parameters can be used to enhance the understandability. The approximate analytical solution can be used as a complement to numerical integration.

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