

Supplementary information

Definition of terms

$X_{ud(segment)}$ = undissolved amount in each GIS chamber or intestinal segment

(s=stomach; d=duodenum; j=jejunum)

$X_{d(segment)}$ = dissolved amount in each GIS chamber or intestinal segment

X_{cen} = amount in central compartment

X_{peri} = amount in peripheral compartment

$V_{segment}$ = volume in each GIS chamber or intestinal segment

$V_{segment,0}$ = initial volume in each GIS chamber or intestinal segment

$k_{sec(segment)}$ = secretion rate constant in each GIS chamber or intestinal segment

$C_{end(s)}$ = final concentration in GIS stomach

F_{sys} = systemic availability;

P_{eff} = effective permeability

k_{12} and k_{21} = central to peripheral and peripheral to central distribution coefficients

R = intestinal radius; 1.5 cm;

DF = degree of flatness; 2;

kt = transit constant from jejunum to distal segments: 0.0056 min⁻¹ (Matsui et al., 2017)

Parameters Z_s ; Z_d ; Z_j i.e dissolution coefficients in each compartment and k_{pre_s} precipitation coefficient in stomach.

Mass Equations for GIS

Undissolved drug in the GIS_{stomach}:

$$\frac{dX_{ud(s)}}{dt} = -Z_s(X_{d(s)} + X_{ud(s)})^{1/3}X_{ud(s)}^{2/3}\left(C_{s(s)} - \frac{X_{d(s)}}{V_s}\right) - \left(-\frac{dV_s}{dt} + k_{sec(s)}\right)\left(\frac{X_{ud(s)}}{V_s}\right) + k_{pre(s)}(X_{d(s)} - C_{end(s)}V_s)$$

Dissolved drug in the GIS_{stomach}:

$$\frac{dX_{d(s)}}{dt} = Z_s(X_{d(s)} + X_{ud(s)})^{1/3}X_{ud(s)}^{2/3}\left(C_{s(s)} - \frac{X_{d(s)}}{V_s}\right) - \left(-\frac{dV_s}{dt} + k_{sec(s)}\right)\left(\frac{X_{d(s)}}{V_s}\right) + k_{pre(s)}(X_{d(s)} - C_{end(s)}V_s)$$

Undissolved drug in the GIS_{duodenum}:

$$\begin{aligned} \frac{dX_{ud(d)}}{dt} = & -Z_d(X_{d(d)} + X_{ud(d)})^{1/3}X_{ud(d)}^{2/3}\left(C_{s(d)} - \frac{X_{d(d)}}{V_d}\right) \\ & + \left(-\frac{dV_s}{dt} + k_{sec(s)}\right)\left(\frac{X_{ud(s)}}{V_s}\right) - \left(-\frac{dV_s}{dt} + k_{sec(s)} + k_{sec(d)}\right)\left(\frac{X_{ud(d)}}{V_d}\right) \end{aligned}$$

Dissolved drug in the GIS_{duodenum}:

$$\begin{aligned} \frac{dX_{d(d)}}{dt} = & Z_d(X_{d(d)} + X_{ud(d)})^{1/3}X_{ud(d)}^{2/3} \left(C_{s(d)} - \frac{X_{d(d)}}{V_d} \right) \\ & + \left(-\frac{dV_s}{dt} + k_{sec(s)} \right) \left(\frac{X_{d(s)}}{V_s} \right) - \left(-\frac{dV_s}{dt} + k_{sec(s)} + k_{sec(d)} \right) \left(\frac{X_{d(d)}}{V_d} \right) \end{aligned}$$

Undissolved drug in the GIS_{jejunum}:

$$\frac{dX_{ud(j)}}{dt} = -Z_j(X_{d(j)} + X_{ud(j)})^{1/3}X_{ud(j)}^{2/3} \left(C_{s(j)} - \frac{X_{d(j)}}{V_j} \right) + \left(-\frac{dV_s}{dt} + k_{sec(s)} + k_{sec(d)} \right) \left(\frac{X_{ud(d)}}{V_d} \right)$$

Dissolved drug in the GIS_{jejunum}:

$$\frac{dX_{d(j)}}{dt} = Z_j(X_{d(j)} + X_{ud(j)})^{1/3}X_{ud(j)}^{2/3} \left(C_{s(j)} - \frac{X_{d(j)}}{V_j} \right) + \left(-\frac{dV_s}{dt} + k_{sec(s)} + k_{sec(d)} \right) \left(\frac{X_{d(d)}}{V_d} \right)$$

$$V_s = V_{s,0} \times e^{-\left(\frac{\ln(2)}{GE}\right)t} \text{ [L]} \quad (\text{if } t > 45 \text{ min, } t = 45)$$

$$V_d = V_{d,0} \text{ [L]}$$

$$V_j = V_{s,0} \times \left(1 - e^{-\left(\frac{\ln(2)}{GE}\right)t} \right) + (k_{sec(s)} + k_{sec(d)}) \times t \text{ [L]} \quad (\text{if } t > 45 \text{ min, } t = 45)$$

$$k_{sec(s)} = 0.001 \text{ [L/min]} \quad (\text{if } t > 45 \text{ min, } k_{sec(s)} = 0)$$

$$k_{sec(d)} = 0.001 \text{ [L/min]} \quad (\text{if } t > 45 \text{ min, } k_{sec(d)} = 0)$$

Mass Equations for in vivo plasma predictions

Undissolved drug in the stomach:

$$\frac{dX_{ud(s)}}{dt} = -Z_s(X_{d(s)} + X_{ud(s)})^{1/3}X_{ud(s)}^{2/3}\left(C_{s(s)} - \frac{X_{d(s)}}{V_s}\right) - \left(-\frac{dV_s}{dt} + k_{sec(s)}\right)\left(\frac{X_{ud(s)}}{V_s}\right) + k_{pre(s)}(X_{d(s)} - C_{end(s)}V_s)$$

Dissolved drug in the stomach:

$$\frac{dX_{d(s)}}{dt} = Z_s(X_{d(s)} + X_{ud(s)})^{1/3}X_{ud(s)}^{2/3}\left(C_{s(s)} - \frac{X_{d(s)}}{V_s}\right) - \left(-\frac{dV_s}{dt} + k_{sec(s)}\right)\left(\frac{X_{d(s)}}{V_s}\right) - k_{pre(s)}(X_{d(s)} - C_{end(s)}V_s)$$

Undissolved drug in the duodenum:

$$\begin{aligned}\frac{dX_{ud(d)}}{dt} = & -Z_d(X_{d(d)} + X_{ud(d)})^{1/3}X_{ud(d)}^{2/3}\left(C_{s(d)} - \frac{X_{d(d)}}{V_d}\right) \\ & + \left(-\frac{dV_s}{dt} + k_{sec(s)}\right)\left(\frac{X_{ud(s)}}{V_s}\right) - \left(-\frac{dV_s}{dt} + k_{sec(s)} + k_{sec(d)}\right)\left(\frac{X_{ud(d)}}{V_d}\right)\end{aligned}$$

Dissolved drug in the duodenum:

$$\begin{aligned}\frac{dX_{d(d)}}{dt} = & Z_d(X_{d(d)} + X_{ud(d)})^{1/3}X_{ud(d)}^{2/3}\left(C_{s(d)} - \frac{X_{d(d)}}{V_d}\right) \\ & + \left(-\frac{dV_s}{dt} + k_{sec(s)}\right)\left(\frac{X_{d(s)}}{V_s}\right) - \left(-\frac{dV_s}{dt} + k_{sec(s)} + k_{sec(d)}\right)\left(\frac{X_{d(d)}}{V_d}\right) - \frac{2DF}{R}X_{d(d)}P_{eff}\end{aligned}$$

Undissolved drug in the jejunum:

$$\begin{aligned}\frac{dX_{ud(j)}}{dt} = & -Z_j(X_{d(j)} + X_{ud(j)})^{1/3}X_{ud(j)}^{2/3}\left(C_{s(j)} - \frac{X_{d(j)}}{V_j}\right) \\ & + \left(-\frac{dV_s}{dt} + k_{sec(s)} + k_{sec(d)}\right)\left(\frac{X_{ud(d)}}{V_d}\right) - k_tX_{ud(j)}\end{aligned}$$

Dissolved drug in the jejunum:

$$\begin{aligned}\frac{dX_{d(j)}}{dt} = & Z_j(X_{d(j)} + X_{ud(j)})^{1/3}X_{ud(j)}^{2/3}\left(C_{s(j)} - \frac{X_{d(j)}}{V_j}\right) \\ & + \left(-\frac{dV_s}{dt} + k_{sec(s)} + k_{sec(d)}\right)\left(\frac{X_{d(d)}}{V_d}\right) - \frac{2DF}{R}X_{d(j)}P_{eff} - k_tX_{d(j)}\end{aligned}$$

Drug in the central compartment:

$$\frac{dX_{cen}}{dt} = \left(\frac{2DF}{R}X_{d(d)}P_{eff} + \frac{2DF}{R}X_{d(j)}P_{eff}\right)F_{sys} - k_{12}X_{cen} + k_{21}X_{peri} - k_eX_{cen}$$

Drug in the peripheral compartment:

$$\frac{dX_{\text{peri}}}{dt} = k_{12}X_{\text{cen}} - k_{21}X_{\text{peri}}$$

Plasma drug concentration:

$$C_p = \frac{X_{\text{cen}}}{V_c}$$

References:

Matsui, K., Tsume, Y., Takeuchi, S., Searls, A., & Amidon, G. L. (2017). Utilization of Gastrointestinal Simulator, an in Vivo Predictive Dissolution Methodology, Coupled with Computational Approach To Forecast Oral Absorption of Dipyridamole. *Molecular Pharmaceutics*, 14(4), 1181–1189. <https://doi.org/10.1021/acs.molpharmaceut.6b01063>