Supporting Information

Mass Equations for GIS

Undissolved drug in the $GIS_{stomach}$:

When $t < t_{lag}$,

$$\frac{dX_{ud(s)}}{dt} = -z_{(s)}(X_{d(s)} + X_{ud(s)})^{1/3}X_{ud(s)}{}^{2/3}\left(C_{s(s)} - \frac{X_{d(s)}}{V_s}\right)$$

When $t >= t_{lag}$,

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

Dissolved drug in the $GIS_{stomach}$:

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

Undissolved drug in the $GIS_{duodenum}$:

When $t < t_{lag}$,

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

When $t >= t_{lag}$,

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

Dissolved drug in the $GIS_{duodenum}$:

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

Undissolved drug in the $GIS_{jejunum}$:

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

Dissolved drug in the $GIS_{jejunum}$:

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

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

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

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

$$k_{sec(s)} = 1 \ [mL/min] \qquad (\text{if } t > 45 \text{ min}, \ k_{sec(s)} = 0)$$

$$k_{sec(d)} = 1 \ [mL/min] \qquad (\text{if } t > 45 \text{ min}, \ k_{sec(d)} = 0)$$

Mass Equations for the GI tract

Undissolved drug in the stomach:

When $t < t_{lag}$,

$$\frac{dX_{ud(s)}}{dt} = -z_{(s)}(X_{d(s)} + X_{ud(s)})^{1/3}X_{ud(s)}{}^{2/3}\left(C_{s(s)} - \frac{X_{d(s)}}{V_s}\right)$$

When $t >= t_{lag}$,

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

Dissolved drug in the stomach:

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

Undissolved drug in the duodenum:

When $t < t_{lag}$,

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

When $t >= t_{lag}$,

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

Dissolved drug in the duodenum:

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

Undissolved drug in the intestine:

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

Dissolved drug in the intestine:

$$\frac{dX_{d(i)}}{dt} = z_{(i)}\left(X_{d(i)} + X_{ud(i)}\right)^{1/3} X_{ud(i)}{}^{2/3}\left(C_{s(i)} - \frac{X_{d(i)}}{V_i}\right) - k_{pre(i)}\left(X_{d(i)} - C_{end(i)}V_i\right) + \left(-\frac{dV_s}{dt} + k_{sec(s)} + k_{sec(d)}\right)\left(\frac{X_{d(d)}}{V_d}\right) - k_{(i-c)}X_{d(i)} - \frac{2DF}{R}X_{d(i)}P_{eff}$$

Fraction escaped from gut metabolism:

$$F_g = 1$$

Fraction escaped from liver metabolism:

$$F_h = \left(1 - \frac{CL_{tot}}{Q_h}\right)$$

Drug in the central compartment:

$$\frac{dX_{cen}}{dt} = \left(\frac{2DF}{R}X_{d(d)}P_{eff} + \frac{2DF}{R}X_{d(i)}P_{eff}\right)F_gF_h - k_{12}X_{cen} - k_{13}X_{cen} + k_{21}X_{peri1} + k_{31}X_{peri2} - k_eX_{cen}$$

Drug in the peripheral compartment 1:

$$\frac{dX_{peri1}}{dt} = k_{12}X_{cen} - k_{21}X_{peri1}$$

Drug in the peripheral compartment 2:

$$\frac{dX_{peri2}}{dt} = k_{13}X_{cen} - k_{31}X_{peri2}$$

Plasma drug concentration:

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

Duodenal drug concentration:

$$C_d = \frac{X_{d(d)}}{V_d}$$

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

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

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

$$k_{sec(s)} = 1 \ [mL/min] \qquad \text{(if } t > 45 \text{ min, } k_{sec(s)} = 0\text{)}$$

$$k_{sec(d)} = 1 \ [mL/min] \qquad \text{(if } t > 45 \text{ min, } k_{sec(d)} = 0\text{)}$$