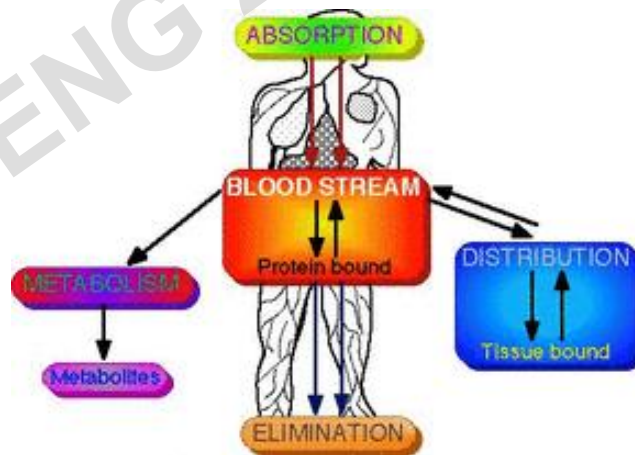
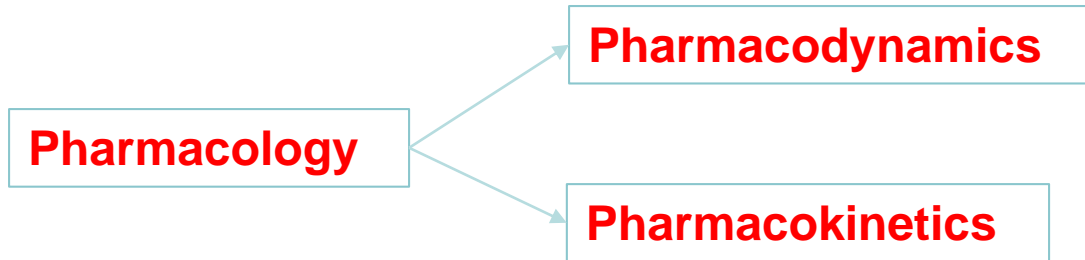


L10. Pharmacokinetics and Biodistribution

May 8, 2018



Pharmacokinetics



Pharmacodynamics (PD) discusses the effect of a drug on the body

- dose dependent relationship
- molecular mechanism of drug activity

Pharmacokinetics (PK) discusses the pathway of a chemical substance from the time it enters the body to the time it is eliminated. It explains the actions of the drug inside the body by **ADME** which comprises four stages:

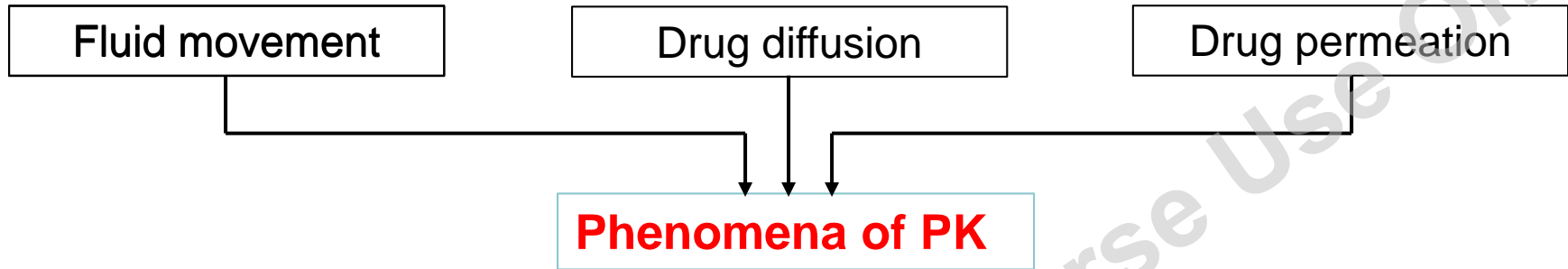
Absorption – It is the route by which the substance enters the blood supply.

Distribution – It involves the distribution of the substance throughout the blood supply.

Metabolism – It is the break-down of the substance into its metabolites.

Excretion – It refers to the elimination of the un-metabolised drug and its metabolites from the body.

Pharmacokinetics



PK is to integrate these isolated basic mechanisms into a functional unit.



Build mathematical models that incorporate description of the uptake, distribution, and elimination of a drug in humans or animals.



Use the models to predict the outcome of different dosage regimens on the time course of drug concentration in tissue.



Compartment models

Physiological models

1. One Compartment Model

Simplest model: A drug/nanoparticle is introduced into a single body compartment, from which it is also eliminated.

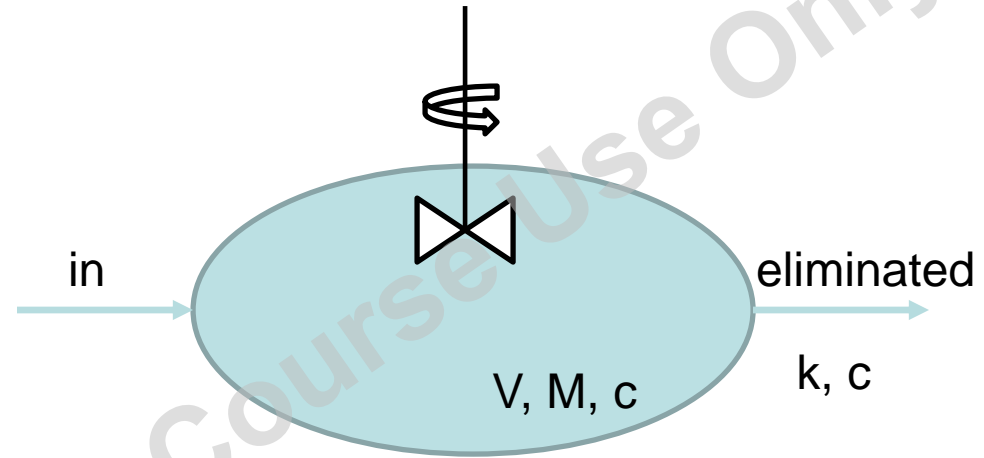
Assumption: first-order elimination

V: compartment volume

M: mass of drug within the compartment, $M = M_0$ at $t = 0$

c: concentration of drug within the compartment

k: first-order elimination constant



1. One Compartment Model

Mass balance:

$$\frac{dM}{dt} = -kM$$

$$M = M_0 e^{-kt} \quad M = c \cdot V$$

$$c = \frac{M_0}{V} e^{-kt} = c_0 e^{-kt}$$

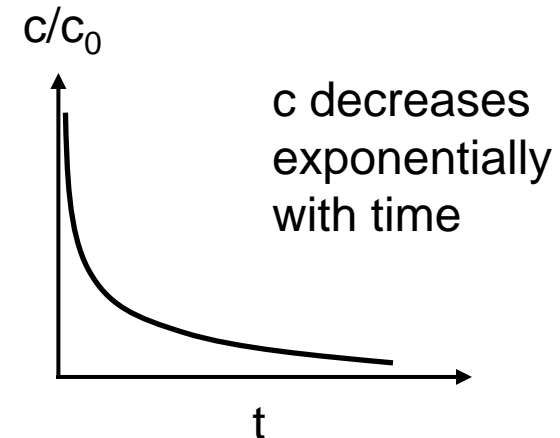
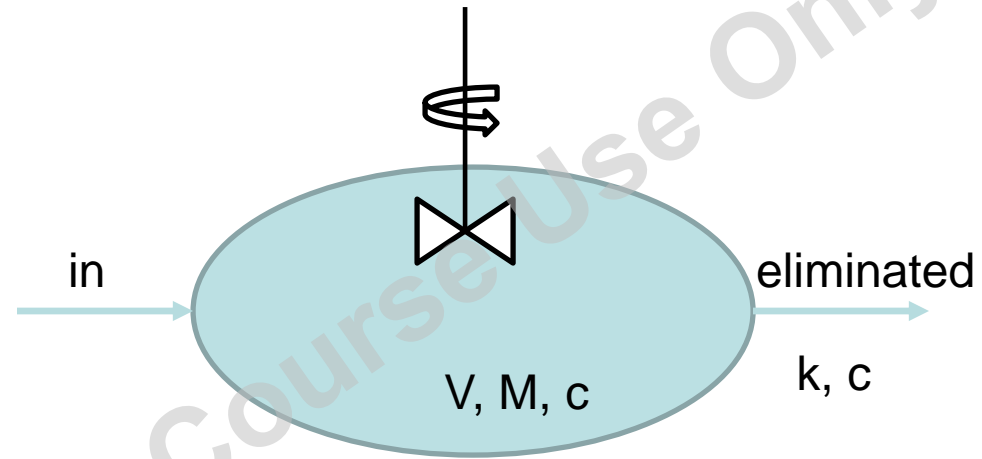
Half-life of drug residence within the compartment: $t_{1/2}$

$$\ln c = \ln \frac{M_0}{V} - kt$$

$$\ln c_0 = \ln \frac{M_0}{V}$$

$$\ln \frac{c_0}{2} = \ln \frac{M_0}{V} - kt_{1/2}$$

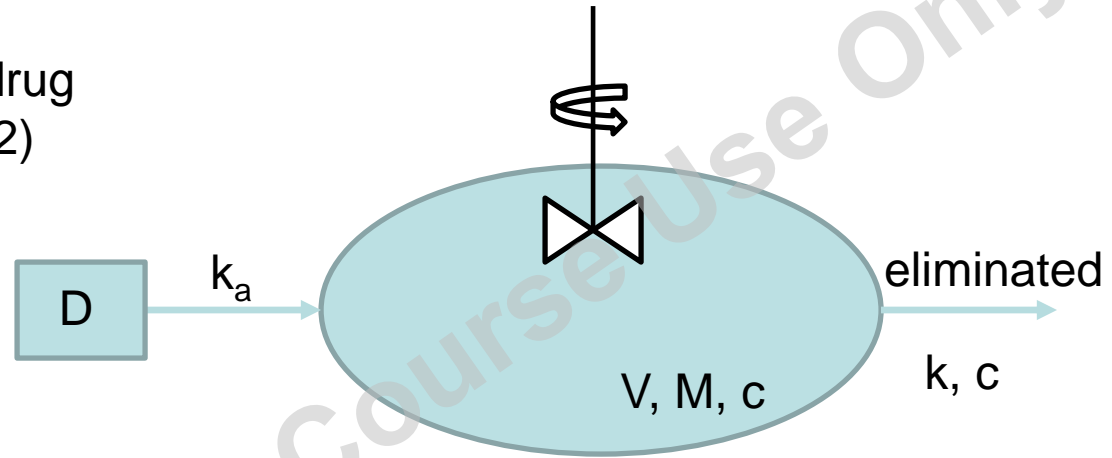
$$t_{1/2} = \frac{\ln 2}{k}$$



Radioisotope- or fluorescence-labeled drug to measure $t_{1/2}$

2. One Compartment Model with Absorption

Absorption of drug: (1) Entry of drug through the gastrointestinal tract; (2) leakage into the circulation after subcutaneous injection.



$$\frac{dM}{dt} = k_a D - kM$$

k_a : first-order absorption constant

D: mass of delivered dose that remains in the absorption compartment

$$\frac{dD}{dt} = -k_a D \quad D = D_0 \text{ at } t = 0$$

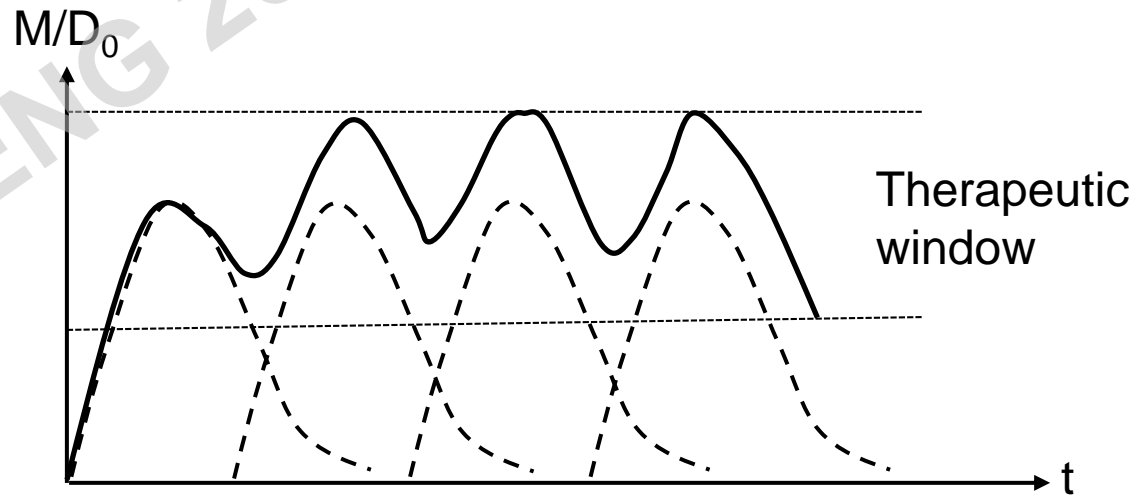
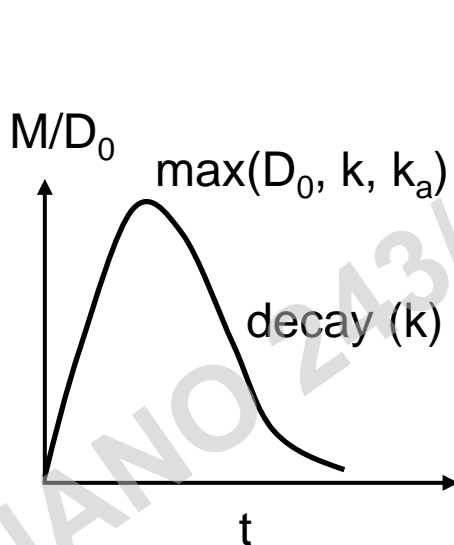
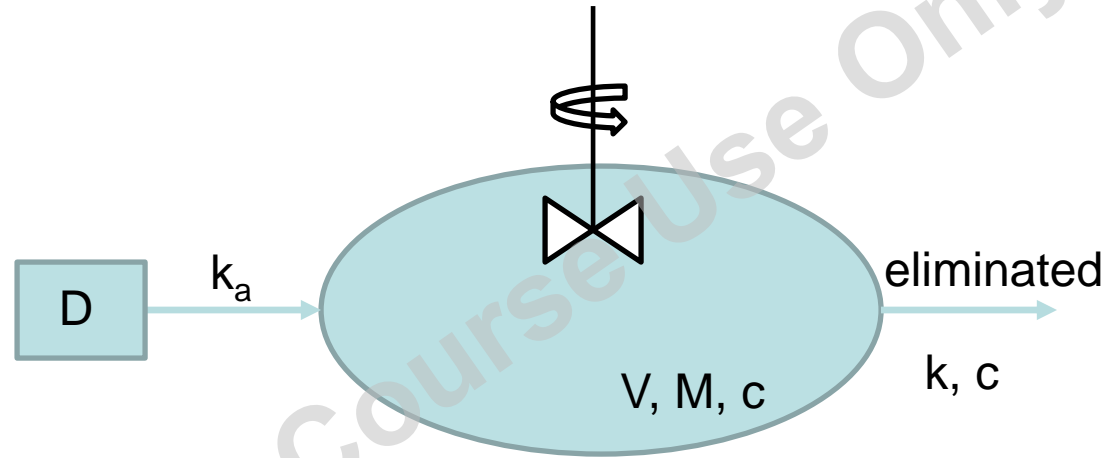
$$D = D_0 e^{-k_a t}$$

2. One Compartment Model with Absorption

$$\frac{dM}{dt} = k_a D_0 e^{-k_a t} - kM$$

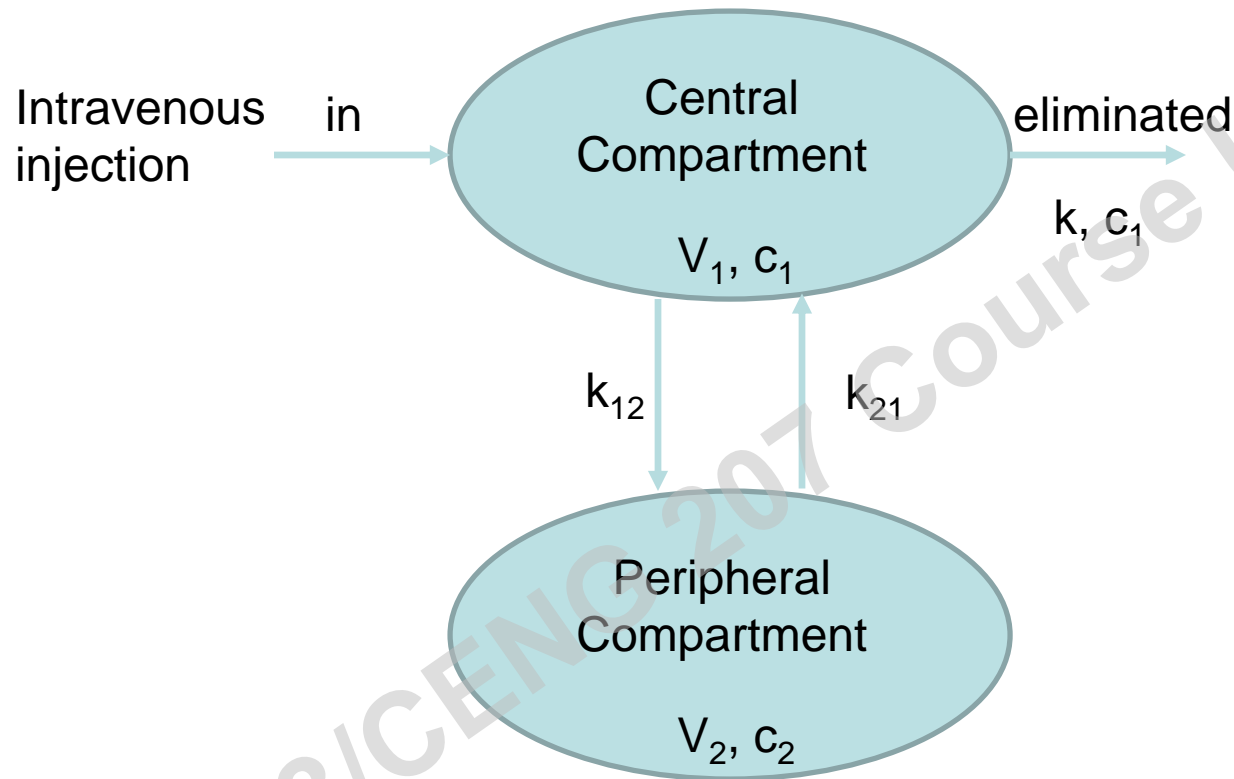
Boundary condition:
 $M = 0$ at $t = 0$

$$M = D_0 \cdot \frac{k_a}{k - k_a} \{e^{-k_a t} - e^{-kt}\}$$



Multiple doses to maintain drug concentration within the therapeutic window.

3. Two Compartment Model



Central compartment: rapidly perfused tissue (e.g. blood)

Peripheral compartment: slowly perfused tissue (e.g. fat, bone)

3. Two Compartment Model

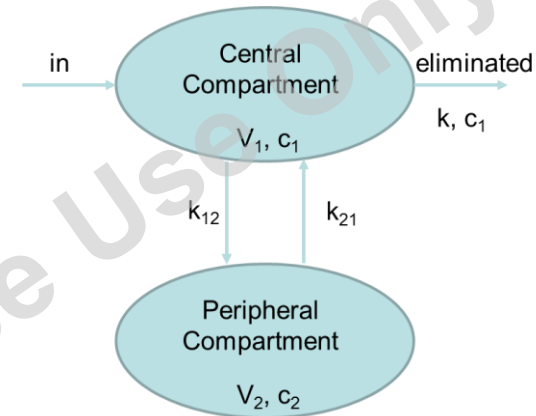
Mass balance on central compartment:

$$V_1 \frac{dc_1}{dt} = k_{21}V_2c_2 - k_{12}V_1c_1 - kV_1c_1$$

Mass balance on peripheral compartment:

$$V_2 \frac{dc_2}{dt} = k_{12}V_1c_1 - k_{21}V_2c_2$$

V_1, V_2 : volume of the central and peripheral compartments, respectively
 c_1, c_2 : drug concentration in the central and peripheral compartments, respectively
 k_{12}, k_{21} : transfer coefficients of drug movement between the two compartments
(If the resistance to drug permeation is the same in both direction,
 $k_{12} = k_{21} = P \cdot A$, permeability X area)
 k : first-order elimination constant from the central compartment



$$c_1 = c_{1,0} \text{ at } t = 0$$

$$c_2 = 0 \text{ at } t = 0$$

3. Two Compartment Model

$$c_1 = Ae^{-\alpha t} + Be^{-\beta t}$$

$$\alpha + \beta = k + k_{12} + k_{21}$$

$$\alpha \cdot \beta = k \cdot k_{21}$$

$$\alpha, \beta = \frac{(k + k_{12} + k_{21}) \pm \sqrt{(k + k_{12} + k_{21})^2 - 4k \cdot k_{21}}}{2}$$

$$A = \frac{c_{1,0}(\alpha - k_{21})}{\alpha - \beta}$$

$$B = \frac{c_{1,0}(k_{21} - \beta)}{\alpha - \beta}$$

$$A + B = c_{1,0}$$

$$c_2 = \frac{V_1}{V_2 k_{21}} [A(\beta - k_{21})e^{-\alpha t} + B(\alpha - k_{12})e^{-\beta t}]$$

3. Two Compartment Model

Elimination from the central compartment occurs in two phases:

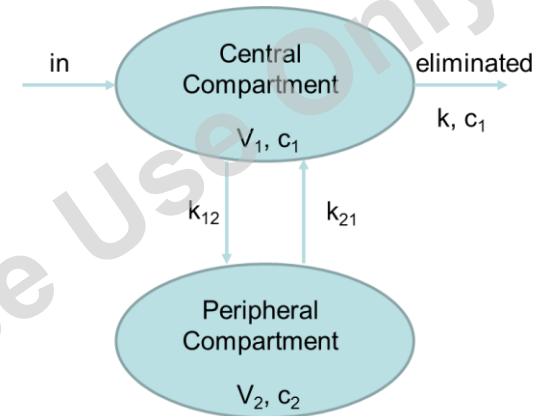
A fast phase with $t_{1/2} = \frac{\ln 2}{\alpha}$

Attributed to drug distribution from the central compartment to peripheral compartment

A slow phase with $t_{1/2} = \frac{\ln 2}{\beta}$

Attributed to drug elimination from the central compartment (biological or terminal half-life)

$$\alpha \gg \beta \Rightarrow t_{1/2}(\alpha) \ll t_{1/2}(\beta)$$



3. Two Compartment Model

Calculate α & β

$$\alpha \gg \beta \quad e^{-\alpha t} \Rightarrow 0, \text{ quickly}$$

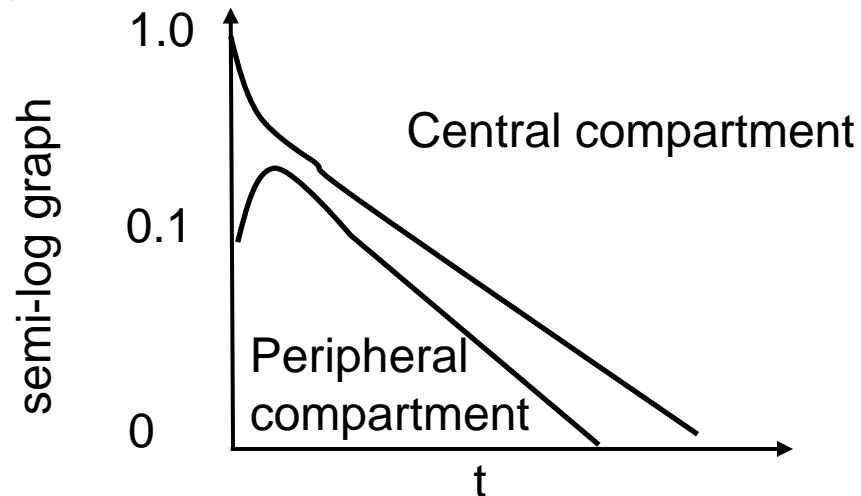
$$c_{1,\text{late}} = Be^{-\beta t}$$

Semi-log graph: $\lg(c_{1,\text{late}}) = \lg B - \beta t$

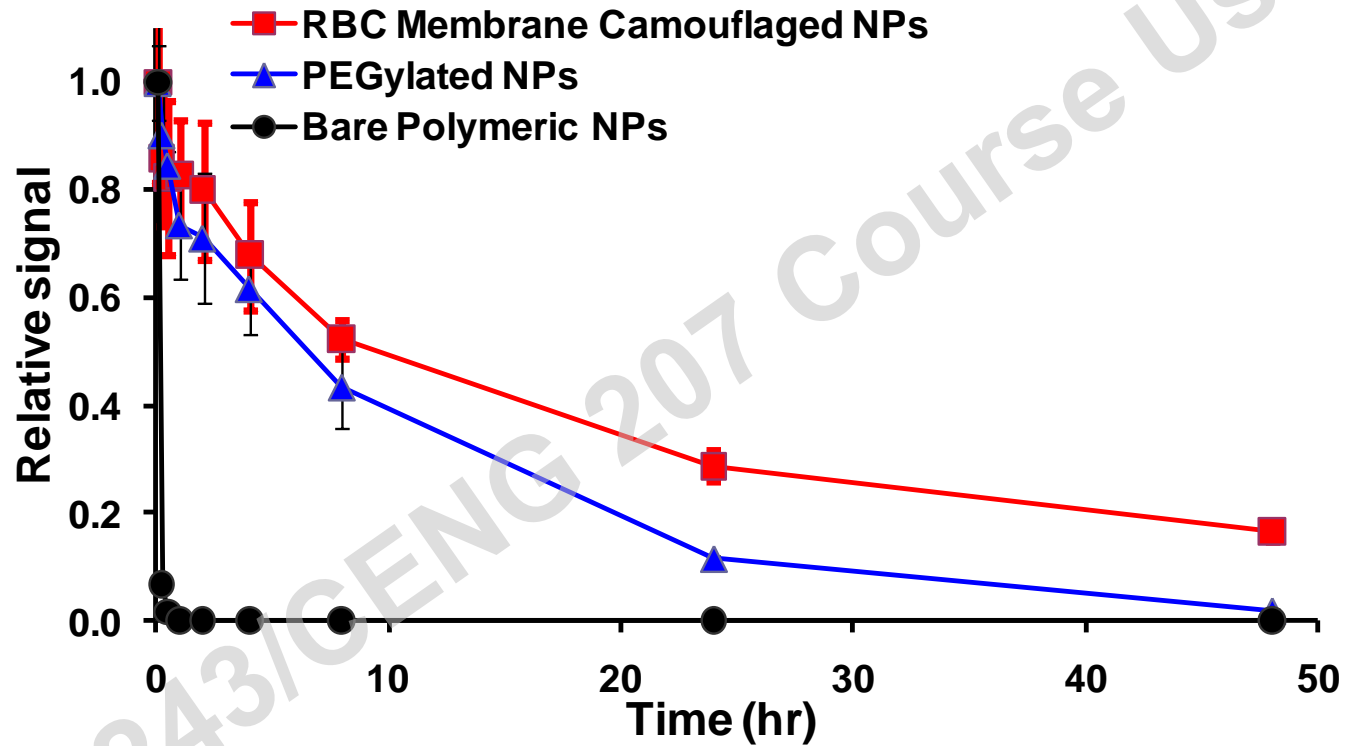
$$\text{Residual} = c_1 - c_{1,\text{late}} = Ae^{-\alpha t}$$

Semi-log graph: $\lg(c_1 - c_{1,\text{late}}) = \lg A - \alpha t$

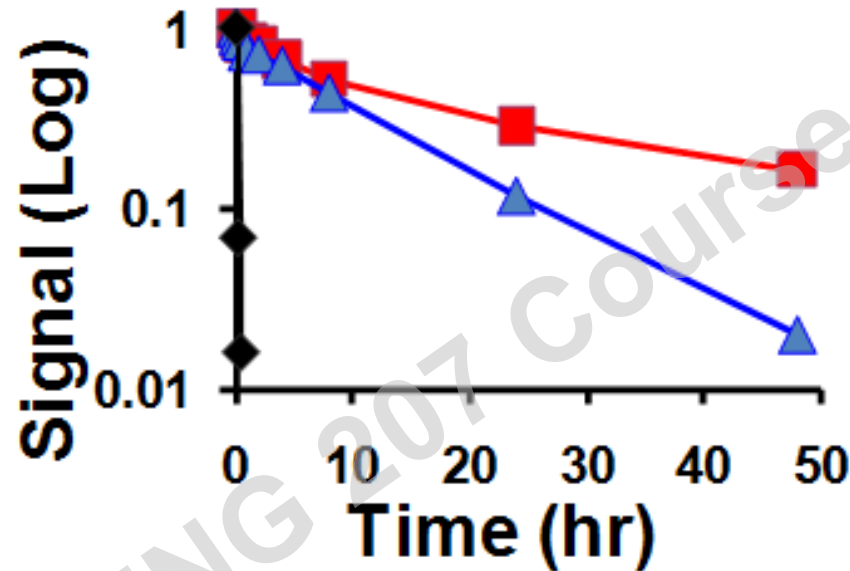
Predicted concentration profile:



4. Example (PK study)



4. Example (PK – Two Compartment Model)



4. Example (Biodistribution)

