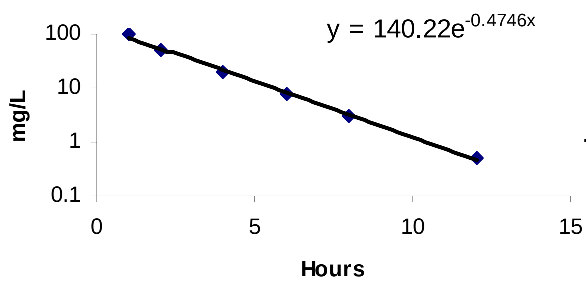
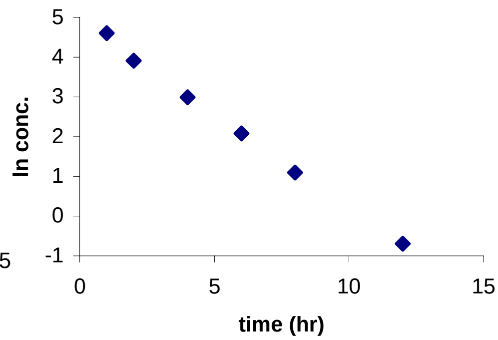
PHA 5127 - Fall 2004
Homework #1

1. A patient was given a 200 mg i.v. bolus of a drug. The following data was obtained.

Time (hr)	Conc. (mg/L)
1	100
2	50
4	20
6	8
8	3
12	0.5

a. Determine if the drug is eliminated by a zero-order or first-order process? Why?





Elimination by a first-order process because the log concentration vs. time plot is linear.

b. Calculate the elimination rate constant and half-life.

See graph above. The slope of the trend line is 0.4746, thus k_e is 0.475 hr^{-1}.
$t_{1/2}$ = 0.693/0.475 = 1.46 hr

or can solve by:

$$k_e = \frac{\ln C_2 - \ln C_1}{t_1 - t_2} = \frac{\ln 100 - \ln 0.5}{12 - 1} = \frac{5.29}{11} = 0.482\ h^{-1}$$

$$t_{1/2} = \frac{0.693}{0.482} = 1.44\ hr$$

c. Determine the initial plasma concentration.

$$C = C_0 * e^{-k_e * t}$$

$$C_0 = \frac{C}{e^{-k_e * t}} = \frac{20}{e^{-0.475*4}} = 133.7\ mg / L$$

d. Calculate the volume of distribution.

$$Vd = \frac{Dose}{C_0} = \frac{200\,mg}{133.7\,mg/L} = 1.50\,L$$

e. Find the $AUC_{0\to\infty}$ using the trapezoidal method.

$$AUC_{0\to t} = \sum\left(\frac{C_n + C_{n+1}}{2} * (t_{n+1} - t_n)\right)$$

$$AUC_{t\to\infty} = \frac{C_{last}}{k_e}$$

Time (hr)	Conc. (mg/L)	AUC mg/L *hr
0	133.7	
1	100	117
2	50	75
4	20	70
6	8	28
8	3	11
12	0.5	7
inf.		1.04
sum		**309.04**

2. Given that a lipophilic drug will readily enter tissue, state how the volume of distribution will change under the following conditions. If not mentioned, assume the other parameters to be fixed.

a. f_u decreases

$$V_p(\leftrightarrow) + V_t(\leftrightarrow)\frac{f_u(\downarrow)}{f_{u,t}(\leftrightarrow)} = Vd(\downarrow)$$

b. $f_{u,t}$ increases

$$V_p(\leftrightarrow) + V_t(\leftrightarrow)\frac{f_u(\leftrightarrow)}{f_{u,t}(\uparrow)} = Vd(\downarrow)$$

c. Both f_u and $f_{u,t}$ decrease by half

$$V_p(\leftrightarrow) + V_t(\leftrightarrow)\frac{f_u(\downarrow)}{f_{u,t}(\downarrow)} = Vd(\leftrightarrow)$$

d. f_u decreases and $f_{u,t}$ increases

$$V_p(\leftrightarrow) + V_t(\leftrightarrow)\frac{f_u(\downarrow)}{f_{u,t}(\uparrow)} = Vd(\downarrow)$$

3. Drug X follows linear one-compartment pharmacokinetics, with a $t_{1/2}$ = 5.3 hours and a V_d = 21 L, calculate a suitable i.v. bolus dose to achieve plasma concentrations of 3 mg/L for 12 hours. What is the initial plasma concentration?

$$k_e = \frac{0.693}{5.3\,hr} = 0.13\,hr^{-1}$$

$$C = C_0 * e^{-k_e * t}$$

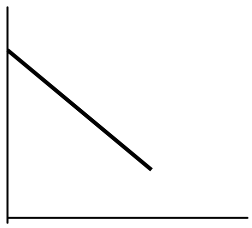
$$C_0 = \frac{C}{e^{-k_e * t}}$$

$$C_0 = \frac{3\,mg/L}{e^{-0.13*12}} = \frac{3\,mg/L}{0.21} = 14.3\,mg/L$$

$$Dose = C_0 * Vd = 14.3\,mg/L * 21\,L = 300.3\,mg \approx 300\,mg$$

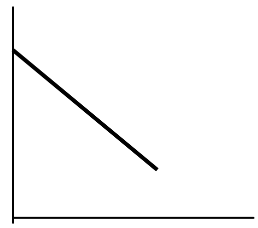
4. Identify which of the graphs below exhibits zero-order and first-order elimination. For which elimination is the half-life dependent on concentration? Write the equations and explain.

ln[drug]



hours

[drug]



hours

The plot on the left shows first-order elimination because it is a semi-log plot that results in a straight line.

$$C = C_0 * e^{-k_e t} \quad C = \frac{C_0}{2} \text{ at } t = t_{1/2}$$

$$\frac{C_0}{2} = C_0 * e^{-k * t_{1/2}}$$

$$\frac{1}{2} = e^{-k * t_{1/2}}$$

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

$$t_{1/2} = \frac{\ln 2}{k} \quad \therefore \text{half} - \text{life is independent on concentration.}$$

The plot on the right shows zero-order elimination because the plot on linear scale results in a straight line.

$$C - C_0 = -k * t$$

$$C = C_0 - k * t \quad C = \frac{C_0}{2} \text{ at } t = t_{1/2}$$

$$\frac{C_0}{2} = C_0 - k * t_{1/2}$$

$$t_{1/2} = (C_0 - \frac{C_0}{2}) / k$$

$$t_{1/2} = \frac{C_0}{2 * k} \quad \therefore \text{half} - \text{life is dependent on concentration.}$$