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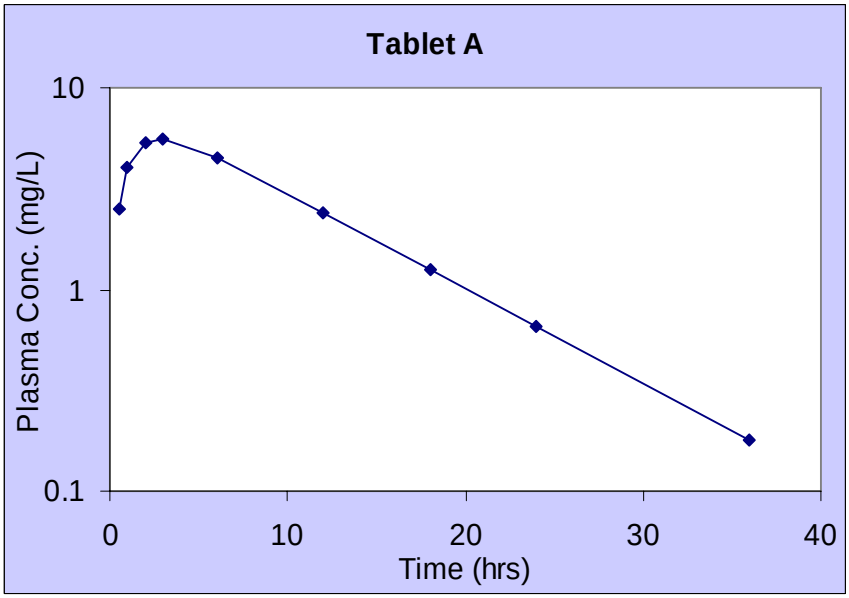
Question 1. A patient is given a 250 mg immediate-release theophylline tablet (Tablet A). A week later, the same patient is given a 250 mg sustained-release theophylline tablet (Tablet B). The tablets follow a one-compartmental model and have a first-order absorption and elimination. The bioavailability is 90% for both tablets. The plasma drug concentration-time profiles for both tablets are as follows:

Time (hrs)	Plasma Drug Conc. (mg/L)	
	Tablet A	Tablet B
0.5	2.52	0.11
1	4.04	0.21
2	5.36	0.39
3	5.56	0.55
6	4.47	0.90
12	2.38	1.23
18	1.26	1.28
24	0.66	1.20
36	0.18	0.93
48		0.68
72		0.34
96		0.16

Determine k_e, k_a, and V_d for both tablets.

Formulation A:

First plot the data on a semi-log scale:



Looking at the plot, we can deduce the following:

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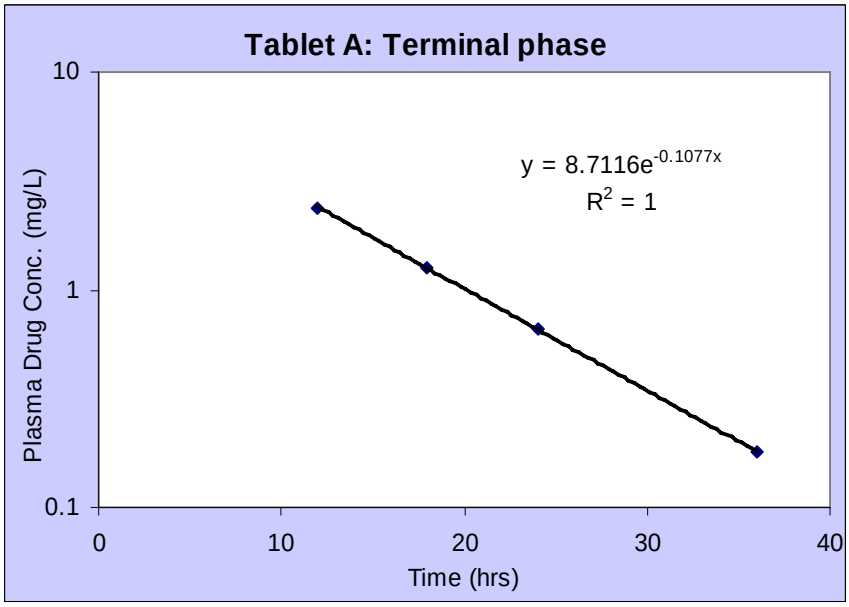
a) The last four data points are fairly linear and assumed to be the terminal phase
b) Since the tablet is an immediate-release one, $k_a >> k_e$ so the terminal phase reflects k_e.

$$Cp = \frac{F \cdot D \cdot k_a}{V_d \cdot (k_a - k_e)} \left(e^{-k_e \cdot t} - e^{-k_a \cdot t} \right)$$

Determine k_e:



Based on the exponential regression of the last four data points:

$Cp'' = C \cdot e^{-k_e \cdot t} = 8.7116 \cdot e^{-0.1077 \cdot t}$

So $k_e = 0.11\ hr^{-1}$

Determine k_a:

We can use the feathering method (also known as method of residuals) to find k_a. Determine Cp" (as shown above) by extrapolating Cp (given in the table on page 1). Find the difference between Cp" and Cp, this will give you (Cp"-Cp). The absorption constant k_a can be determined from the exponential regression of (Cp"–Cp).

Time (hrs)	Cp (mg/mL)	Cp" (mg/mL)	Cp"-Cp (mg/mL)
0.5	2.52	8.3	5.7
1	4.04	7.8	3.8
2	5.36	7.0	1.7
3	5.56	6.3	0.7

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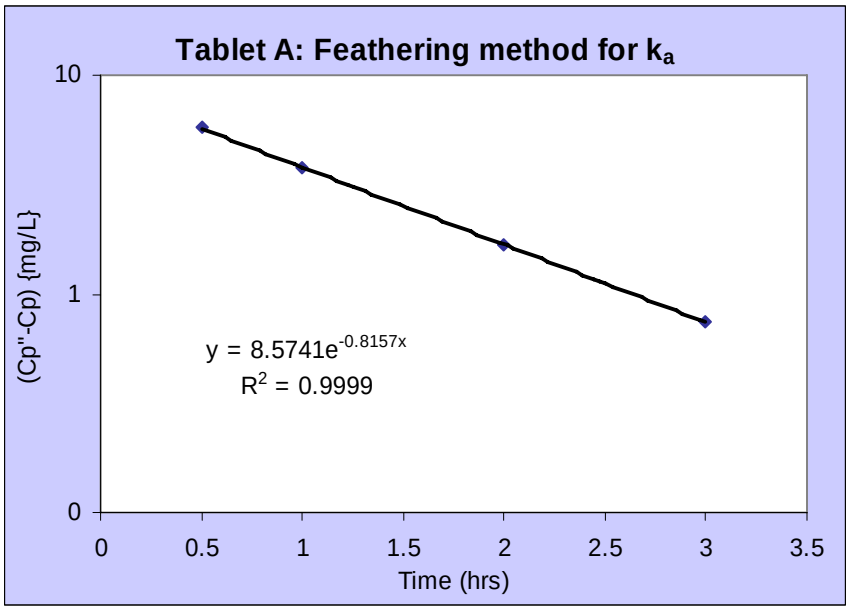

From the regression: $(Cp"–Cp) = C \cdot e^{-k_a \cdot t} = 8.5741 \cdot e^{-0.8157 \cdot t}$
So, $k_a = 0.82\ hr^{-1}$.

Determine V_d:

From the terminal phase regression line, V_d can be determined from the constant C.

$$C = \frac{D \cdot F \cdot k_a}{V_d \cdot (k_a - k_e)}$$

$$8.71 \, mg/L = \frac{250mg \times 0.9 \times 0.82hr^{-1}}{V_d \cdot (0.82hr^{-1} - 0.11hr^{-1})} = \frac{260mg}{V_d}$$

$$V_d = \frac{260mg}{8.71 \, mg/L} = 30L$$

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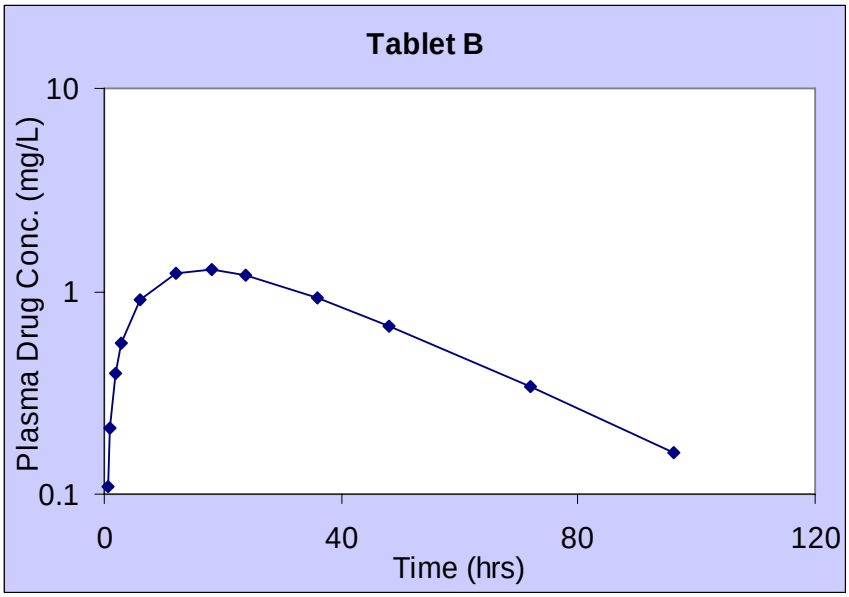
Formulation B:

First plot the data on a semi-log scale:

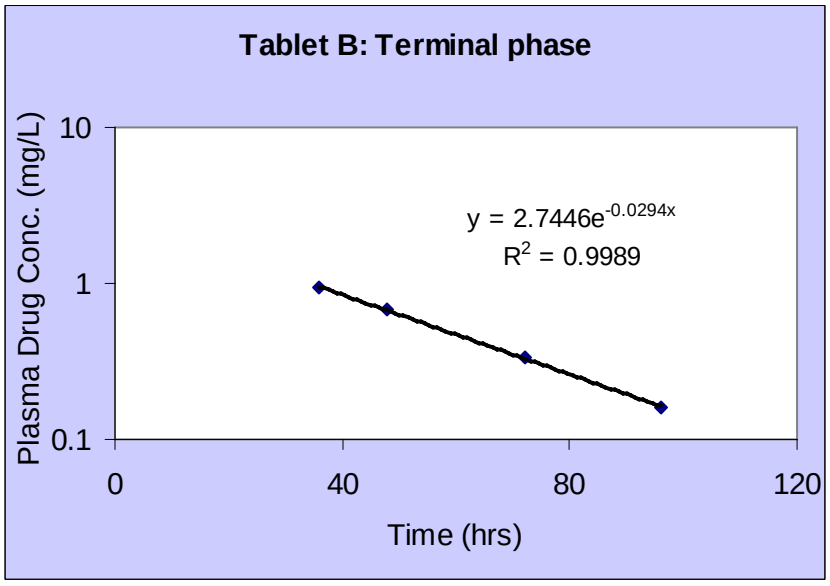


Looking at the plot, we can deduce the following:

c) The last four data points are fairly linear and assumed to be the terminal phase
d) Since the tablet is a sustained-release one, $k_a << k_e$ (we have a flip-flop situation) so the terminal phase reflects k_a.

Please note that in the case of a flip-flop situation, $Cp = \frac{F \cdot D \cdot k_a}{V_d \cdot (k_e - k_a)} \left(e^{-k_a \cdot t} - e^{-k_e \cdot t} \right)$.

Determine k_a:



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Based on the exponential regression of the last four data points:

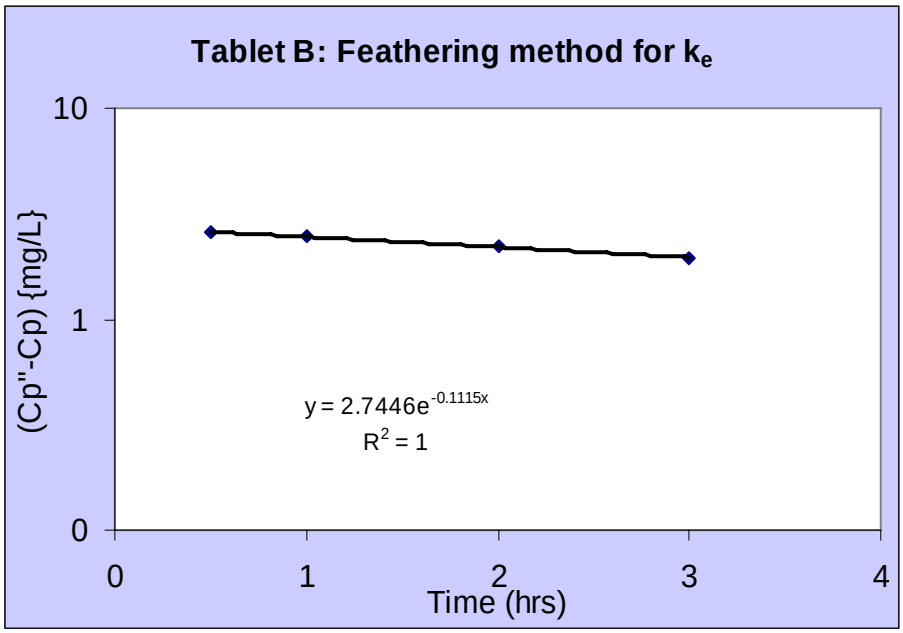
$Cp'' = C \cdot e^{-k_a \cdot t} = 2.7446 \cdot e^{-0.0294 \cdot t}$

So $k_e = 0.029\ hr^{-1}$

Determine k_e:

We can use the feathering method to find k_e. Determine Cp" (as shown above) by extrapolating Cp (given in the table on page 1). Find the difference between Cp" and Cp, this will give you (Cp"-Cp). The absorption constant k_e can be determined from the exponential regression of (Cp"–Cp).

Time (hrs)	Cp (mg/mL)	Cp" (mg/mL)	Cp"-Cp (mg/mL)
0.5	0.11	2.7	2.6
1	0.21	2.7	2.5
2	0.39	2.6	2.2
3	0.55	2.5	2.0



From the regression: $(Cp''-Cp) = C \cdot e^{-k_e \cdot t} = 2.7446 \cdot e^{-0.1115 \cdot t}$

So, $k_e = 0.11\ hr^{-1}$.

Determine V_d:

From the terminal phase regression line, V_d can be determined from the constant C.

$$C = \frac{D \cdot F \cdot k_a}{V_d \cdot (k_e - k_a)}$$

$$2.74 \, {}^{mg}\!/\!_{L} = \frac{250mg \times 0.9 \times 0.029hr^{-1}}{V_d \cdot (0.11hr^{-1} - 0.029hr^{-1})} = \frac{80.6mg}{V_d}$$

$$V_d = \frac{80.6mg}{2.74 \, {}^{mg}\!/\!_{L}} = 29.4L$$

Question 2. For a one-compartment, first-order absorption and elimination, multiple oral administration, state whether the follows parameters will increase, decrease, or no change. (Hint: Use simulation files to answer this question)

$$C_{ss,avg} = \frac{F \cdot D}{CL \cdot \tau} \qquad F = \frac{C_{ss,\max}}{C_{ss,\min}} \qquad t_{ss,\max} = \frac{\ln\left(\frac{k_a\left(1 - e^{-k_e \cdot \tau}\right)}{k_e\left(1 - e^{-k_a \cdot \tau}\right)}\right)}{k_a - k_e}$$

$$t_{1/2abs} = \frac{\ln(2)}{k_a}$$

Parameters used: D = 250 mg, τ = 6 hrs, n = 4, $t_{1/2abs}$ = 2hrs, V_d = 30 L, CL = 30 L/hr

	$C_{ss,avg}$	Fluctuation, F	t_{max}
CL in halved	Doubled	Decreased	Increased since k_e is halved
τ is doubled	Halved	Increased	Increased
F is halved	Halved	No change	No change
k_a is doubled	No change	Increased	Decreased

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Question 3. A patient is to be put on a continuous iv infusion. Devise a dosing regimen (including a loading dose) for the patient. (Assume the drug to follow a one-compartment model and has a first-order elimination). Following are the properties of the drug and the patient:

Patient Weight	130 lbs
Drug's half-life ($t_{1/2}$)	3 hrs
Volume of distribution (V_d)	1.8 L/kg
Desired average steady state concentration (C_{ss})	7.5 μg/mL

$$k_o = C_{ss} \cdot CL = C_{ss} \cdot k_e \cdot V_d = \frac{C_{ss} \cdot V_d \cdot \ln(2)}{t_{1/2}}$$

$$k_o = \frac{7.5\,\mu g/mL \cdot \left(1.8\,L/kg \times \frac{1000mL}{1L} \times 130lbs \times \frac{1kg}{2.2lb}\right) \cdot \ln(2)}{3hrs} \cdot \left(\frac{1mg}{1000\mu g}\right) = 184\,mg/hr$$

$$Loading\ Dose = C_{ss} \cdot V_d = 7.5\,\mu g/mL \cdot \left(1.8\,L/kg \times \frac{1000mL}{1L} \times 130lbs \times \frac{1kg}{2.2lb}\right) \cdot \left(\frac{1mg}{1000\mu g}\right)$$

$$Loading\ Dose = 798mg$$

Question 4. True and False

1. The absorption rate constant (k_a) is always larger than the elimination rate constant (k_e). FALSE

2. The oral bioavailiability of a very lipophilic, neutral, high extraction drug (showing linear pharmacokinetics) after oral administration of a tablet is significantly affected by the liver blood flow, the plasma protein binding, and the dissolution rate. TRUE

3. Cp_{max} and t_{max} are sufficient to assess bioequivalency. FALSE

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Question 5. Fill in the blanks

1. If $k_a << k_e$ for a drug administered orally (typical of a sustained release formulation), the drug is said to follow "_flip-flop_" kinetics.

2. The method of residuals, also known as "_feathering_", is means by which k_e and k_a may be separated and calculated when oral data is analyzed.

3. The _bioavailability_ is the fraction of an oral dose that enters systemic circulation after administration.

4. Once a constant rate infusion is started, the time required to reach steady state levels is dependent on the _half-life_ (multiplied by 5) of the drug.