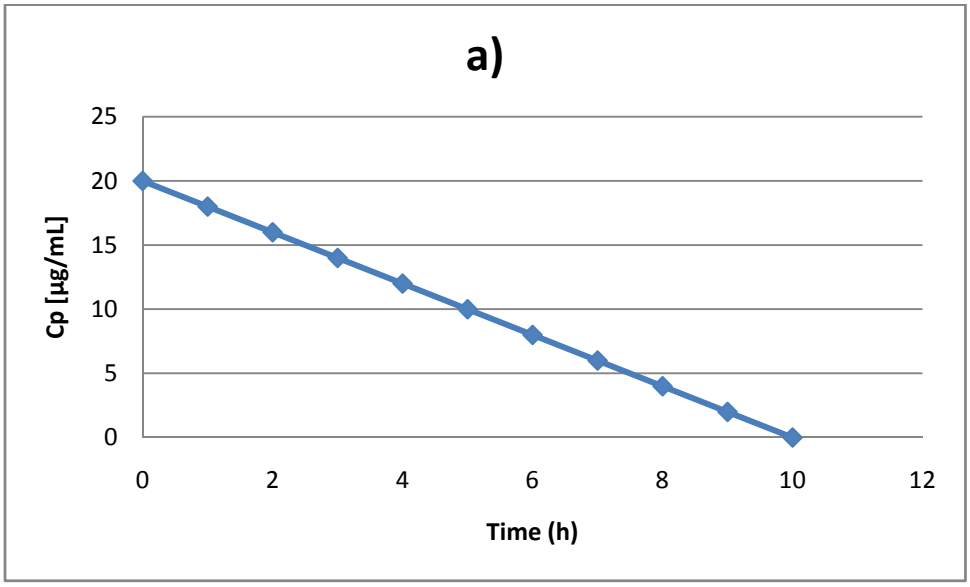
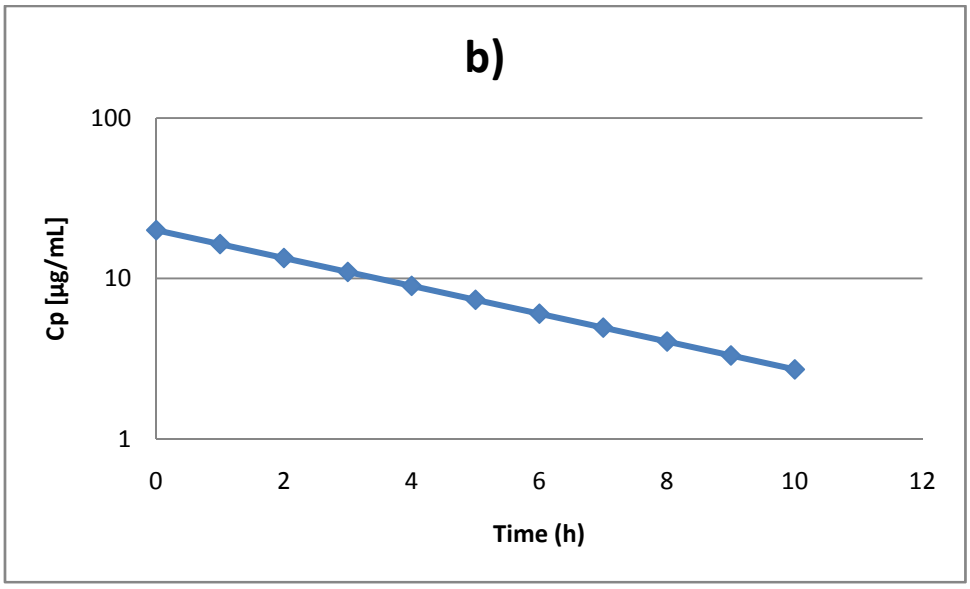
PHA 5127 Dose Optimization I

Case Study I

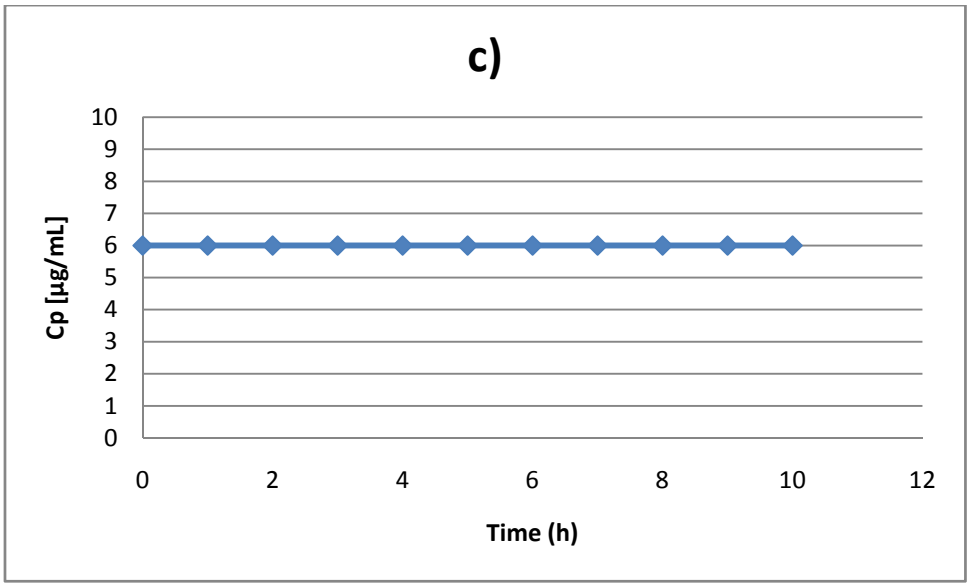
1. **Determine whether the elimination process in the graphs a-d is zero-order or first order. (Cp: Drug concentration in plasma)**



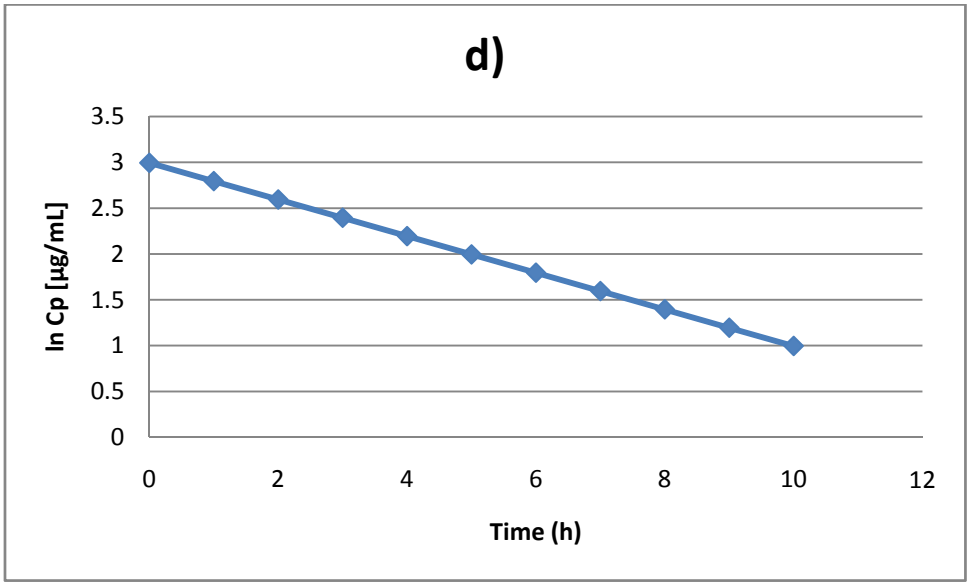
Zero-order (straight line)



First-order (straight line after semilogarithmic transformation of the y-axis)



No Elimination

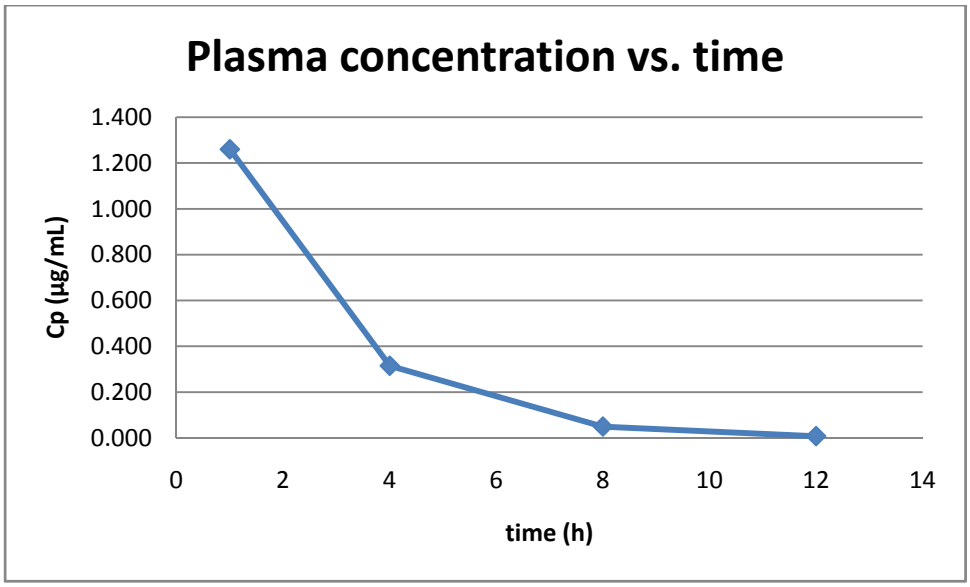


First-order (straight line after semilogarithmic transformation of the plasma concentrations)

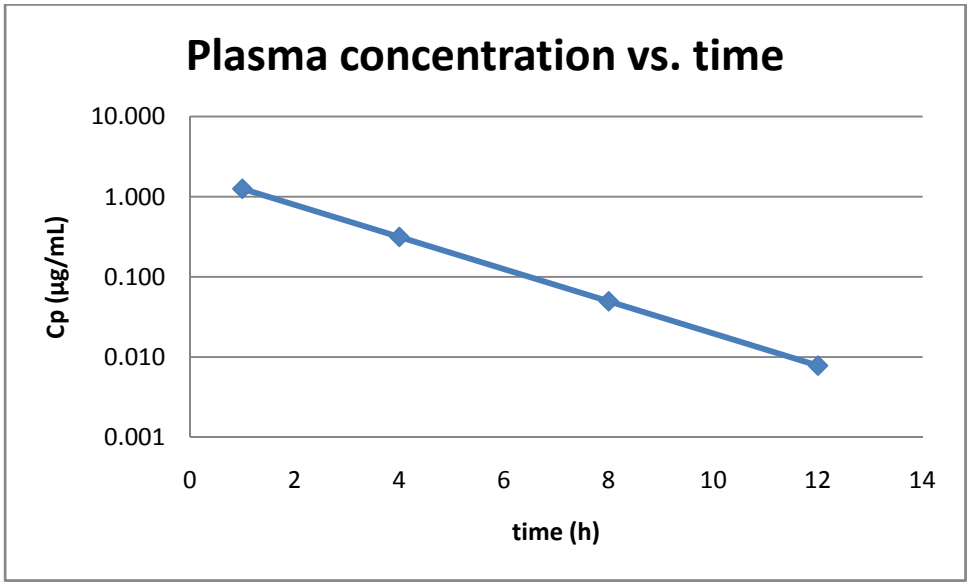
2. **200 mg Drug A was administered to a female patient (60 kg) through IV bolus injection. The following plasma concentrations (Cp) were observed.**

time (h)	Cp (µg/mL)
1	1.260
4	0.315
8	0.050
12	0.008

a) Plot Cp vs. time and determine the order of the elimination process



Semilogarithmic transformation of the y-axis



Plasma concentration vs. time profile is a straight line after semilogarithmic transformation. Thus, the elimination process is a first-order process.

b) Determine k_e and $t_{1/2}$ (half life)

time (h)	Cp (µg/mL)	ln Cp ( )
0	2.000	0.6931
1	1.260	0.2310
4	0.315	-1.1552
8	0.050	-3.0036
12	0.008	-4.8520

$$Slope = \frac{-1.1552 - 0.2310}{4 - 1\ h} = -0.4621\ \frac{1}{h}$$

$$k_e = 0.4621\ \frac{1}{h}$$

$$t_{1/2} = \frac{\ln(2)}{k_e} = 1.5\ h$$

c) Estimate the initial concentration C_0 and the volume of distribution (Vd)

$$C(t) = C_O * e^{-k_e * t}$$

$$\ln C(t) = ln\ C_O - k_e * t$$

$$ln\ C_O = \ln C(t) + k_e * t$$

$$ln\ C_O = \ln C(1) + k_e * 1$$

$$ln\ C_O = 0.2310 + 0.4621 * 1 = 0.6931$$

$$C_O = e^{0.6931} = 2.00\ \frac{\mu g}{mL}$$

$$C_O = \frac{Dose}{Vd}$$

$$Vd = \frac{200\ mg}{2.00\ \mu g/mL} = 100\ L$$

d) Calculate $AUC_{0\text{-}t(last)}$ and $AUC_{0\text{-}\infty}$ (Use trapezoidal rule)

time (h)	Cp (µg/mL)	AUC (µg*h/mL)
0	2.000	1.63
1	1.260	2.36
4	0.315	0.73
8	0.050	0.11
12	0.008	

$AUC_{0\text{-}t(last)} = (1.63 + 2.36 + 0.73 + 0.11)$ µg*h/mL = 4.83 µg*h/mL

$$AUC_{t(last)-\infty} = \frac{C_{t(last)}}{k_e} = \frac{0.008\ \mu g/mL}{0.4621\ 1/h} = 0.0173\ \mu g*h/mL$$

$$AUC_{0-\infty} = (4.83 + 0.0173)\ \mu g * h/mL = 4.847\ \mu g*h/mL$$

e) Calculate $\frac{AUC_{0-t(last)}}{AUC_{0-\infty}} * 100\%$

$$\frac{4.83\ \mu g * h/mL}{4.847\ \mu g * h/mL} * 100\% = 99.65\%$$

f) Predict the plasma concentration after 6 hours

$$C(6) = 2.00\ \frac{\mu g}{mL} * e^{-0.4621\,\frac{1}{h}*6\,h} = 0.125\ \frac{\mu g}{mL}$$

3. Define **LADME** and **Pharmacokinetics**

LADME: Liberation, Absorption, Distribution, Metabolism, Elimination

Pharmacokinetics: The time course of drug and metabolite concentration in the body

4. TRUE (T) or FALSE (F)

The plasma concentration time profile of a certain drug is dependent on the dosage form

T **F**

For a zero-order elimination process, the half-life is dependent on the plasma concentration at time point 0 (C_0)

T **F**

For a first-order elimination process, the half-life is dependent on the plasma concentration at time point 0 (C_0)

T **F**

Drugs with a high volume of distribution (Vd) have a narrow therapeutic window

T **F**

In the case of perfusion limited distribution, the blood flow determines the rate of uptake

T **F**

In the case of permeability limited distribution, the blood flow is not important for the rate of uptake

T **F**