PHA 5127

Case Study #1 Solution

Question #1.

Penicillin G was made in three different formulations.

A. Injectable Aqueous Solution

B. Injectable Oil

C. Injectable Oil+Aluminum Stearate

The same dose (200mg) of Penicillin G product in different formulations was given to a healthy subject. The design of this clinical study is given below:

Period I		Period II		Period III
Penicillin G (aqueous solution, 200mg, I.V bolus)	Wash Out (2 weeks)	Penicillin G (oil, 200mg, I.M)	Wash Out (2 weeks)	Penicillin G (oil + aluminum stearate, 200mg, I.M)

The respective plasma concentration vs. time profiles are collected and shown in Figure. 1.

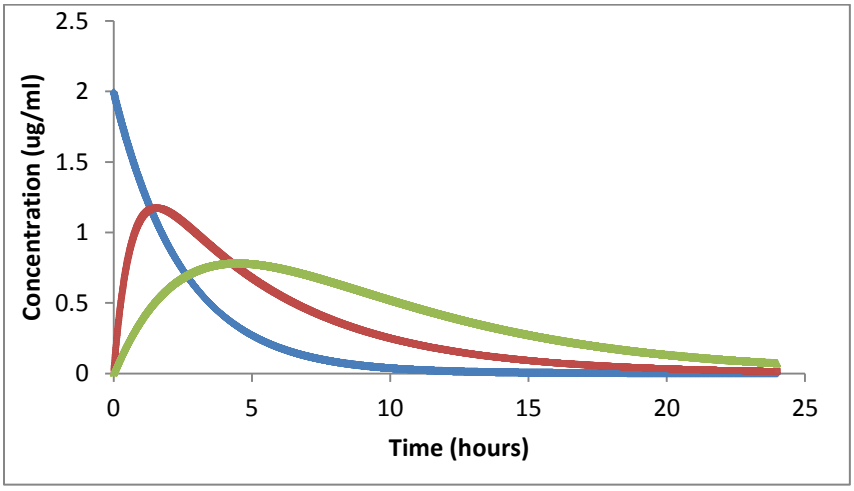


Fig. 1

1.1. Based on the information above, please match each plasma concentration vs. time profile to its correspondent formulation on the graph. Explain your choice.

Injectable Aqueous Solution: blue curve

Injectable Oil: red curve

Injectable Oil+Aluminum Stearate: green curve

It is clear that the blue curve is the I.V bolus injection because absorption is not involved, the drug distributed immediately right after the administration. Both oil and oil+aluminum stearate are administered through I.M, they both have the absorption phase. The oil prevents contact of drug with aqueous medium thereby slowing down dissolution and absorption, the aluminum stearate further delays dissolution and absorption by increasing viscosity, thus the red curve should be the injectable oil, and the green curve is the injectable oil +aluminum stearate.

1.2. If Penicillin G has a therapeutic window of 0.5 ug/ml – 1.5 ug/ml, which formulation should be considered based on the information provided?

Injectable oil+aluminum stearate

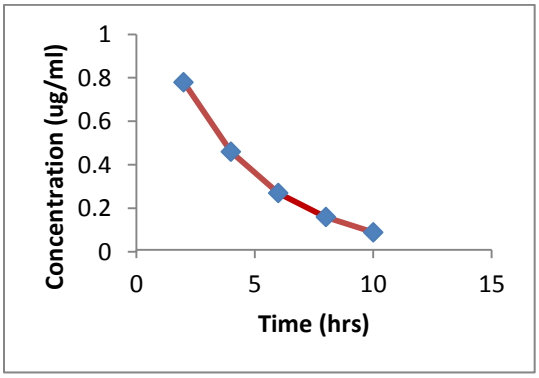
Question #2.

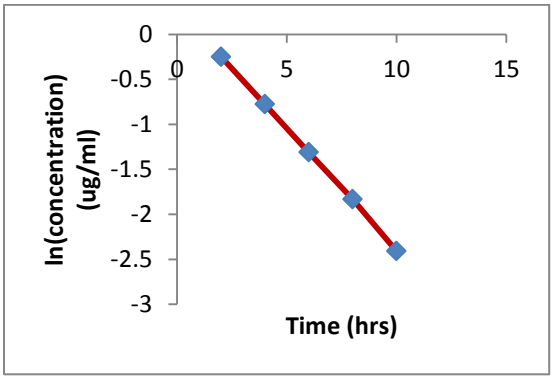
200mg Drug A was administered to a patient through i.v bolus injection. His plasma drug concentrations were measured at 5 different time points. The data is summarized in Table.1 below.

Table.1

Time (h)	Plasma Conc (ug/ml)
2	0.78
4	0.46
6	0.27
8	0.16
10	0.09

2.1. Is the elimination process zero order or first order? Show your work.





After plotting the data, we could see that plasma concentration vs. time profile shows a curve on a linear scale, but it shows a straight line on a semi-log scale, therefore, the elimination process is first order.

2.2. Determine the elimination rate constant K_e and half-life ($t_{1/2}$).

$$K_e = -\frac{\ln C_2 - \ln C_1}{t_2 - t_1} = -\frac{\ln 0.46 - \ln 0.78}{4-2} = 0.264\ h^{-1}$$

$$t_{1/2} = \frac{0.693}{K_e} = \frac{0.693}{0.264} = 2.63\ h$$

2.3. Calculate the initial plasma drug concentration.

$$Conc = C_0 \cdot e^{-k_e t} \Rightarrow C_0 = \frac{Conc}{e^{-k_e t}} = \frac{0.78}{e^{-0.264 \cdot 2}} = 1.32\ \text{ug/ml}$$

2.4. Calculate the volume of distribution V_d.

$$V_d = \frac{Dose}{C_0} = \frac{200}{1.32} = 151.5\ \text{L}$$

2.5. Use trapezoidal rule to calculate the area under the curve $AUC_{0\to\infty}$

$$AUC_{0\to\infty} = AUC_{0\to last} + AUC_{last\to\infty}$$

$$AUC_{0\to last} = \frac{(1.32+0.78)\times(2-0)}{2} + \frac{(0.46+0.78)\times(4-2)}{2} + \frac{(0.27+0.46)\times(6-4)}{2}$$

$$+\frac{(0.16+0.27)\times(8-6)}{2} + \frac{(0.09+0.16)\times(10-8)}{2} = 4.75\ \text{ug}\cdot\text{h/ml}$$

$$AUC_{last\to\infty} = \frac{C_{last}}{K_e} = \frac{0.09}{0.264} = 0.34\ \text{ug}\cdot\text{h/ml}$$

$$AUC_{0\to\infty} = 4.75 + 0.34 = 5.09\ \text{ug}\cdot\text{h/ml}$$

2.6. What is the plasma drug concentration after 12 hours?

$$C_{12h} = C_0 \cdot e^{-k_e t} = 1.32 \cdot e^{-0.264 \cdot 12} = 0.056\ \text{ug/ml}$$

Question #3.

3.1. **T** F The plasma concentration time profile of a certain drug is dependent on the dosage form.

3.2. T **F** For a zero-order elimination process, the rate of elimination is dependent on the amount of the drug.

3.3. T **F** For a one-compartment body model first-order elimination process, plasma concentration vs. time profile after an i.v bolus shows a straight line on a linear scale.

3.4. **T** F Instantaneous distribution to body tissues and fluids is assumed in one-compartment body model.