PHA 5127 Dose Optimization I

Case Study VI

1. A hypertensive patient is going to receive long-term medication of drug A. Drug A can only be administered via IV-bolus injection due to its low oral bioavailability. The volume of distribution and clearance of drug A are 120 L and 10 L/h, respectively. Drug A's plasma protein binding is 30%. Drug A is known to show severe side effects if its free plasma concentration is higher than 5µg/mL. In order to avoid these side effect and to reach an antihypertensive effect, the Drug A's maximum free drug concentration at steady state should be 20% less than 5µg/mL. The patient has agreed to come twice a day to hospital for the administration of the drug. The physician asks you as a clinical pharmacist to calculate the dose that should be administered to the patient. Which assumptions did you make to ensure that your calculations are valid?

$$f_u = 0.7$$

$$0.8 * C_{SS,free} = 0.8 * 5\frac{\mu g}{mL} = 4\frac{\mu g}{mL}$$

$$f_u = \frac{C_{SS,free}}{C_{SS,total}}$$

$$C_{SS,total} = \frac{C_{SS,free}}{f_u} = \frac{4\frac{\mu g}{mL}}{0.7} = 5.714\frac{\mu g}{mL}$$

$$k_e = \frac{CL}{VD} = \frac{10L/h}{120L} = 0.0833\ \frac{1}{h}$$

$$r_{ss} = \frac{1}{(1 - e^{-k_e * \tau})}$$

$$r_{ss} = \frac{1}{\left(1 - e^{-0.0833\ \frac{1}{h} * 12h}\right)} = \frac{1}{0.632} = 1.582$$

$$Cmax_{SS,total} = \frac{Dose}{VD} * r_{ss}$$

$$Dose = \frac{VD * Cmax_{SS,total}}{r_{ss}}$$

$$Dose = \frac{120\ L * 5.714\frac{mg}{L}}{1.582} = 433.426\ mg\ \approx 433\ mg$$

- Linear pharmacokinetics
- First-order elimination processes
- One-compartment-body model

2. Another patient receives the same drug (drug A) as a single-dose IV-bolus injection to treat his hypertensive crisis. A metabolite of drug A is known to counteract the effect of another drug that the patient receives. Thus, a physician asks you as a clinical pharmacist to predict the plasma concentration of the metabolite 6 hours after the administration of the drug A. Assume that 500 mg of drug A will be administered and that the elimination rate constant of the metabolite after IV-bolus injection is 5 h^{-1} (k_{met} = 0.04 h^{-1}, VD_M = VD).

$$C_P^M = \frac{k_{met} * Dose}{VD_M * (k_e^M - k_e)} * \left(e^{-k_e * t} - e^{-k_e^M * t}\right)$$

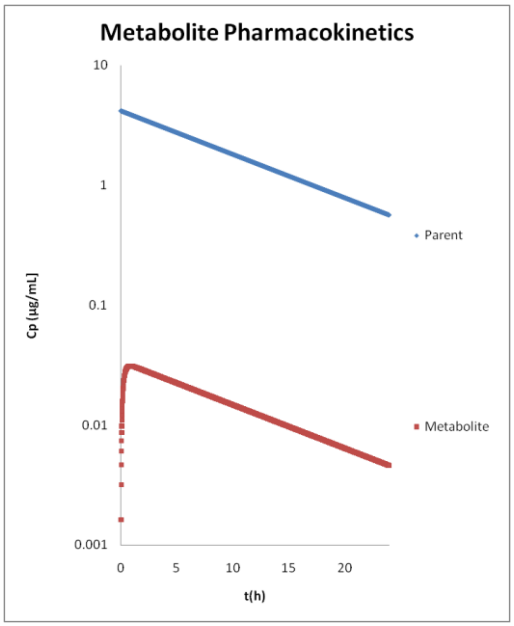
$$C_P^M = \frac{0.04\frac{1}{h} * 500mg}{120L * (5\frac{1}{h} - 0.0833\frac{1}{h})} * \left(e^{-0.0833\frac{1}{h} * 6h} - e^{-5\frac{1}{h} * 6h}\right)$$

$$= \frac{20\frac{mg}{h}}{590.004\frac{L}{h}} * 0.6067 = 0.02057\frac{mg}{L} = 0.02057\frac{\mu g}{mL}$$

Calculate the total amount of metabolite that has been eliminated. Assume the metabolite is solely cleared by the kidney (no further metabolism).

$$= \frac{k_{met}}{k_e} * Dose = \frac{0.04\ \frac{1}{h}}{0.083\ \frac{1}{h}} * 500\ mg = 240.964\ mg$$

Sketch a semi-logarithmic plot of the plasma concentration time profile of drug A and its metabolite.



Would this sketch change tremendously if the elimination rate constant of the metabolite was doubled? If yes, sketch the new semi-logarithmic plot of the plasma-concentration-time-profile.

The sketch would not change tremendously.

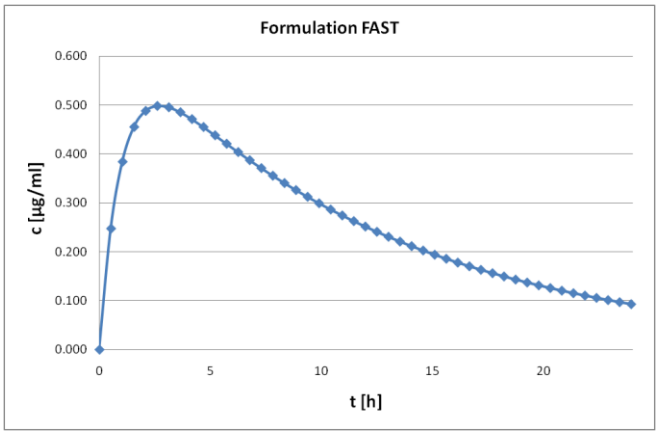
$$k_e^M \gg k_e$$

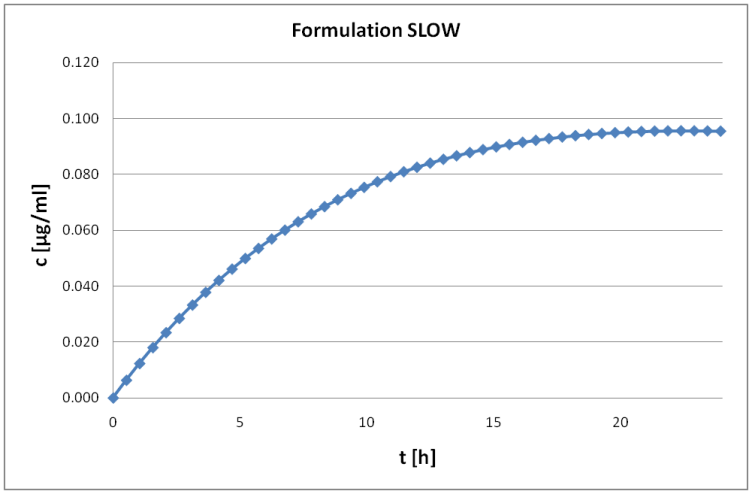
Hence, for the terminal phase

$$C_P^M = \frac{k_{met} * Dose}{VD_M * (k_e^M - k_e)} * (e^{-k_e * t})$$

Terminal phase will reflect k_e which does not change.

3. A company has invented a formulation technique that has increased the oral bioavailability of drug A to 15%. Due to this new possibility two differently formulated tablets have come on the market. The absorption rate constants of formulation FAST and SLOW are 1 h^{-1} and 0.02 h^{-1}, respectively. Plot the concentration-time-profile from 0-24 h for both formulations. Which formulation shows a "flip-flop"-kinetic?





4. TRUE (T) or FALSE (F)

For multiple-dosing, the free plasma concentration at steady state is always dependent on the clearance of the drug

T **F**

It generally takes about five half-lives for a drug to be cleared from the body after steady state has been reach.

T **F**

For multiple-dosing, the peak-through-fluctuation is independent of the dose only after oral administration of the drug

T **F**

The average concentration at steady state can be calculated as

$$\frac{Dose}{VD * F}$$

T **F**

For a one compartment body model and oral administration, K_e cannot be calculated as

$$\frac{C_0}{AUC_\infty}$$

T **F**

After oral administration, T_{max} can always be calculated as

$$\frac{ln\left(\frac{k_e}{k_a}\right)}{k_e - k_a}$$

T **F**