1. Show the change of AUC of any drug given orally if the protein binding is increased. Assume that the drug undergoes hepatic first pass metabolism. Hint: $F = 1 - E$,

$$E = \frac{CL_{\text{int}} \cdot f_u}{Q + CL_{\text{int}} \cdot f_u}$$

AUC depends on the amount of dose absorbed into systemic circulation and clearance.

$$AUC = \frac{F \cdot D}{CL}$$

Assuming that first-pass effect and clearance are due to hepatic processes,

$$F = 1 - E = 1 - \frac{CL_{\text{int}} \cdot f_u}{Q + CL_{\text{int}} \cdot f_u} = \frac{Q}{Q + CL_{\text{int}} \cdot f_u}$$

$$CL_{\text{int}} = \frac{Q \cdot CL_{\text{int}} \cdot f_u}{Q + CL_{\text{int}} \cdot f_u}$$

$$AUC = \frac{Q}{Q + CL_{\text{int}} \cdot f_u} \cdot D \cdot \left( \frac{Q + CL_{\text{int}} \cdot f_u}{Q \cdot CL_{\text{int}} \cdot f_u} \right) = \frac{D}{CL_{\text{int}} \cdot f_u}$$

2. A patient (m, 35y, 74 kg) with a subtherapeutic theophylline (5 μg/mL) is admitted to the ICU. Based on average pharmacokinetics parameters ($V_d = 0.5 \text{ L/kg}$, $t_{1/2} = 8 \text{ h}$), calculated an i.v. bolus loading dose and a maintenance dose (i.v. infusion) to increase the level to 15 μg/mL.

$$V_d = 74 \cdot 0.5 = 37 \text{ L}$$

$$LD = (15 - 5) \cdot 37 = 370 \text{ mg}$$

$$CL = (0.639/8) \cdot 37 = 3.2 \text{ L/h}$$

$$MD = 15 \cdot 3.2 = 48 \text{ mg/h} \text{ or } 1152 \text{ mg/d}$$
3. A drug has a total body clearance of 45 mL/min and a volume of distribution of 35 L. It is completely absorbed. The therapeutic range is 10-20 μg/ml. Make a dosing recommendation for chronic use.

Cl\text{tot} = 45 \text{ ml/min}, \ Vd = 35 \text{ L}

Recommend a dosing regimen for achieving concentrations in the therapeutic range of 10-20 μg/ml.

Since the problem states the drug is completely absorbed, we will assume that an oral dosing regimen is needed.

We will also assume that the drug is fast-absorbing and IV bolus equations are sufficient to determine dose and dosing interval.

Start by finding \( \tau \):

\[
\tau = \frac{\ln[Cpss(max) / Cpss(min)]}{k_e}
\]

\(Cpss(max) = 20 \mu g/ml\)

\(Cpss(min) = 10 \mu g/ml\)

\(k_e\) may be calculated from Cl and Vd

\[
k_e = \frac{CL}{Vd} = \frac{45 \text{ ml/min}}{35 L} \cdot \frac{1L}{1000 ml} \cdot \frac{60 \text{ min}}{1 hr} = 0.077 hr^{-1}
\]

The dosing interval is then:

\[
\approx = \frac{\ln(20/10)}{0.077 hr^{-1}} = 9 hr \approx 8 hr
\]

At steady-state, maximum plasma concentrations are:

\[
Cpss(max) = \frac{D}{Vd \cdot (1 - e^{-k_e \cdot \tau})}
\]

So Dose

\[
D = Cpss(max) \cdot Vd \cdot (1 - e^{-k_e \cdot \tau})
\]

\[
= (20 \mu g/ml) \cdot (35 L) \cdot (1 - e^{-(0.077 hr^{-1}) \cdot 8 hr}) \cdot \frac{1000 ml}{L} \cdot \frac{1 mg}{1 \mu g} = 322 mg
\]

This dosage would be rounded to a more convenient number depending on the tablets available.
4. A drug tablet (S=0.62, with bioavailability F = 0.7) follows one-compartmental pharmacokinetics and has a total body clearance of 2.5 L/hr and a volume of distribution of 50 L. The oral absorption rate constant \( k_a \) is 0.4 /hr. Calculate the \( T_{max} \), \( C_{max} \), AUC if a 250 mg tablet is taken.

Give \( V_d=50 \text{ L} \) \( CL=2.5 \text{L/hr-1} \) \( ka=0.4 \text{hr-1} \)

\[
k_e = \frac{CL}{V_d} = \frac{50}{2.5} = 0.05 \text{hr}^{-1}
\]

\[
T_{max} = \frac{\ln(k_a / k_e)}{(k_a - k_e)} = 5.9 \text{hr}
\]

\[
C_{max} = \frac{D \cdot S \cdot F \cdot k_a}{V_d \cdot (k_a - k_e)} \cdot (e^{-k_e T_{max}} - e^{-k_a T_{max}}) = 1.6 \text{mg/L}
\]

or

\[
C_{max} = \frac{D \cdot S \cdot F}{V_d} \cdot e^{-k_e T_{max}} = 1.6 \text{mg/L}
\]

\[
AUC = \frac{D \cdot S \cdot F}{CL} = 43.4 \text{mg \cdot hr/L}
\]

5. Please mark the following questions with TRUE (T) or FALSE (F):

(T) (F) For an oral drug, it is possible that the metabolite has a shorter terminal half-life than the parent drug.

(T) (F) In general, in bioequivalence studies blood is collected for 3 or more terminal half lives.

(T) (F) In general, a multiple dose BE study for modified release dosage forms is not recommended.

(T) (F) The AUC extrapolated to time infinity for the first dose is equal to steady-state AUC values over a single dosing day at steady state.

(T) (F) In general, bioequivalence study is required for all strengths if the strengths are proportionally similar and meet dissolution profile comparison criteria.