PHA-5127 Dose Optimization

Case Study 1 Due: September 2nd

1) In characterizing the food effects (for regulatory purposes) on the extent of drug absorption, the FDA requires the drug firms to conduct human pharmacokinetic studies in healthy subjects. In such studies the investigator administers the drug to healthy subjects with and without food and determines any changes in Cmax, Tmax, and AUC.

   A drug X is under consideration. The drug is weakly acidic and has a **pKa of 4.0**. The drug was administered orally as a tablet to healthy volunteers under fasting (without food) and fed (with food) conditions. The figure below shows the plasma concentration time profiles (mean profile of the subjects) and the table shows the actual mean data collected from both conditions.

   (Hint: The gastric emptying time is delayed with food)

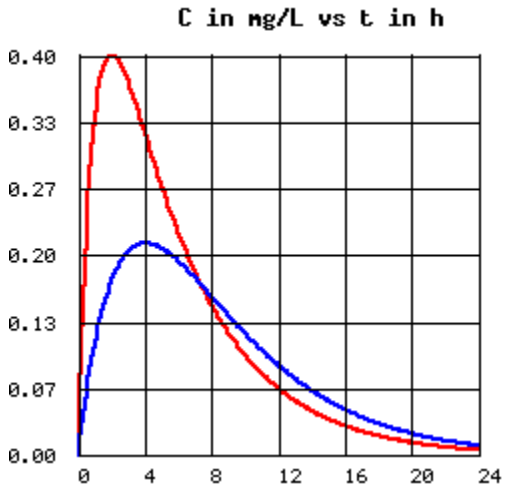

Figure: Y axis: Plasma Concentration (mg/L)

X axis: time (hr)

Mean profiles of the subjects under **fasting (red)** and **fed (blue)** state.

Table: Plasma Concentration (mg/L) and time (hr) data for the fasting and the fed conditions

Fed State		Fasting State	
time(hr)	**conc(mg/L)**	time(hr)	conc(mg/L)
0.00	**0.00**	0.00	0.00
0.10	**0.01**	0.10	0.06
0.20	**0.03**	0.20	0.11
0.40	**0.05**	0.40	0.19
0.60	**0.07**	0.60	0.25
0.80	**0.09**	0.80	0.30
1.00	**0.11**	1.00	0.34
2.00	**0.17**	2.00	0.40
3.00	**0.20**	3.00	0.37
4.00	**0.21**	4.00	0.32
6.00	**0.20**	6.00	0.22
8.00	**0.16**	8.00	0.15
10.00	**0.12**	10.00	0.10
12.00	**0.09**	12.00	0.07
14.00	**0.07**	14.00	0.05
16.00	**0.05**	16.00	0.03
18.00	**0.03**	18.00	0.02
20.00	**0.02**	20.00	0.01
22.00	**0.02**	22.00	0.01
24.00	**0.01**	24.00	0.01

a) Calculate the AUC (0-24hr) (Area under the curve for time 0-24hr) for both the fasting and the fed conditions (Use the trapezoidal rule.) MS Excel can be used for calculations.

Ans: Fasting condition – AUC (0-24hr) – 2.9688 mg*hr/L

Fed Condition - AUC (0-24hr) – 2.3364 mg*hr/L

b) Report the Cmax and the tmax (the maximum concentration and the time to maximum concentration) under the fasting and the fed conditions as observed from the data.

Ans: Fasting Condition – Cmax: - 0.40 mg/ L at time 2.00 hr

Fed Condition - Cmax: - 0.21 mg/L at time 4.00hr

c) Is the rate of absorption faster in the fasting or the fed state? Explain? (Hint: The rate is reflected in the parameters Cmax and Tmax. Use the Hendersson Hasselbach equation to determine the fraction ionized for the drug at the stomach pH (1 to 3) and the intestinal pH (5-7))

Ans: The rate of absorption is faster in the fasting conditions compared to the fed conditions. Using the Henderson-Hasselbach equation for weak acids we can see that weak acids are more ionized at higher pH (pH >4) than when compared to lower pH values. This suggests that the drug might have a higher solubility at intestinal pH compared to stomach pH. Therefore, in fed conditions due to the delay in gastric emptying time, the rate of absorption is slower.

d) Is the extent of absorption different in the fasting and fed state? If yes, what could be the potential reasons?

(Hint: The extent of absorption is reflected in the AUC)

Ans: The extent of absorption is affected in fed conditions, which is reflected as a lower AUC compared to the fasting conditions. One possible explanation could be that the drug might be unstable in stomach conditions. Due to the delay in gastric emptying time the bioavailability is reduced in fed state.

True or False

1) Drugs that are lipophilic and small usually exhibit permeability limited distribution? (T/F)
2) A drug that has extremely high tissue binding will definitely have a large volume of distribution? (T/F)
3) The plasma concentration time profile of a certain drug is dependent on the dosage form. (T/F)