UNIVERSITY OF RUHUNA – FACULTY OF MEDICINE

ALLIED HEALTH SCIENCES DEGREE PROGRAMME

FOURTH B. PHARM PART II EXAMINATION –JULY 2016

PH 4242: BIOPHARMACEUTICS (SEQ)

TIME: TWO HOURS

INSTRUCTIONS

- Answer all questions.
- No paper should be removed from the examination hall.
- Do not use any correction fluid.
- Use illustrations where necessary.

1. Physicochemical properties of three drugs are shown in the table given below.

Compound	pKa	Log p
Indometacin	3.91	3.5
Progesterone	-	3.8
Dipyridamole	6.20	1.6

pKa: negative log of the acid dissociation constant
p : partition coefficient

1.1. Discuss the solubility patterns of the three drugs in the stomach and the duodenum with reference to the pKa values. ***(20 marks)***

1.2. Describe the absorption characteristics of three drugs given in the table? ***(15 marks)***

1.3. Briefly explain the elimination of three drugs given in the table? ***(10 marks)***

1.4. Concomitant intake of ethanol is known to alter the solubility and absorption characteristics of immediate release formulations of above drugs. Following table shows the general pharmacokinetic parameters of these drugs in fasted state following oral absorption. Ethanol is believed to be reduce the gastric emptying time while working as co-solvent in the stomach. Ethanol also reduce the dielectric constant of the mixture. Considering these factors answer following questions.

Compound	AUC(ng.hr/ml)	C_{max} (ng/ml)	T_{max}(hr)	Fab_{abs}(%)
Indometacin	16,728	7824	1.2	100
Progesterone	24,262	4283	3.3	44
Dipyridamole	23.61	1.906	5.9	1.7

1.4.1.

AUC: Area under the curve

C_{max} : maximum concentration

T_{max}: time taken to reach the maximum concentration

20

1.4.1. Comment on T_{max} of indometacin, progesterone and dipyridamole with concomitant intake of 20% ethanol. Justify your answer. (5 marks)

1.4.3. Draw three graphs for three drugs to compare the current AUC and the predicted AUC in the presence 20% ethanol. **(30 marks)**

Note: no need to use graph papers

1.5. First pass metabolism of ethanol occurs in the gut wall by alcohol dehyrogenases. In the liver it is metabolized by CYP2EI liver enzyme. If theophylline and paracetamol is metabolized by the same liver enzyme. State the effect of concomitant intake of drugs given in the table with ethanol. **(10 marks)**

2. The absorption, distribution and elimination characteristics of a model drug "CRPII" have been extensively studied. The drug is known to be highly protein bound.

2.1. Describe how extensive protein binding affects the elimination of "CRPII" via renal route. **(15 marks)**

2.2. List two (02) factors that govern the uptake and accumulation of a drug into tissue. **(10 marks)**

2.3. Define the terms "perfusion rate limited" and "permeability rate limited" **(10 marks)**

2.4. If drug CRPII distribution is permeability rate limited, describe how the extravascular fluid distribution of this drug is altered in an oedemic condition. **(15 marks)**

2.5. Using Fick's law of diffusion describe how sink conditions are achieve during drug absorption and distribution. **(10 marks)**

2.6. Briefly describe the William's dichotomy of metabolic reactions using examples. **(30 marks)**

2.7. Describe how you would determine relative and absolute bioavailability of above mentioned new drug entity (CRPII). **(10 marks)**

3.

3.1. Briefly explain two assumptions made in one compartment model. **(10 marks)**

3.2 What is relative bioavailability? **(10 marks)**

3.3. Define 'apparent volume of distribution' (V) in an equation. **(10 marks)**

3.4.

3.4.1. Convert the below equation in to logarithms. **(5 marks)**

$$C = C_o\ e^{-kt}$$

3.4.2. Derive $t_{1/2} = 0.693 / k$ using the above relationship. **(15 marks)**

3.5. Below table contains plasma drug concentrations after an IV bolus injection of 500mg of an active drug substance.

Time (Hours)	C_p (mg/dl)
2	4.8
4	0.8

C_p = plasma drug concentration.

Assuming first order kinetics, determine;

3.5.1. Rate of elimination (K) ***(20 marks)***

3.5.2. C_o (Initial drug concentration in plasma) ***(10 marks)***

3.5.3. Volume of distribution ***(20 marks)***

4. .

4.1. What is the rule 5 in relation to the drug absorption and permeation? ***(10 marks)***

4.2. Fill in the blanks in the table below in relation to biopharmaceutical classification system. ***(10 marks)***

Class I Highly permeable …….. soluble	Class…….. Highly permeable Poorly soluble
Class III …… permeable ……soluble	Class IV …….. permeable Poorly soluble

4.3. According to the Food and Drug Administration (FDA), define the term high solubility. ***(10 marks)***

4.4. A 35 year-old, 55 kg male had been advised to commence gentamicin, 80 mg IV bolus 8 hourly. Gentamicin levels in his blood (C_p) after the first dose were determined as follows.

Time (Hours)	C_p (mg/L)
1	4.5
4	2.3

4.4.1. Calculate the elimination rate constant. ***(15 marks)***

4.4.2. Determine the elimination half-life. ***(10 marks)***

4.4.3. Calculate the volume of distribution. ***(15 marks)***

4.5. The data of a drug (A) infusion is given as follows.

Elimination rate constant (k) = 0.80 mg/dl Hr

Volume of distribution (V) = 25 dl

4.5.1. Calculate the clearance of drug (A). ***(10 marks)***

4.5.2. Calculate the maintenance dosing rate if the steady state expected is 10 mg/dl. ***(10 marks)***

4.5.3. Determine the elimination half-life of drug (A). ***(10 marks)***