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PHARMACY 324 PHARMACOKINETICS
Term #1 EXAM December 10th, 2004

Examination time is 3 hours

[This examination contains 14 pages (not including equations and graph paper)]

BUDGET YOUR TIME! WATCH THE VALUE OF THE QUESTIONS!
PLEASE PLACE YOUR NAME ON EACH PAGE

Please read the ensuing examination questions and data provided carefully before attempting any calculations. **Show all your calculations**. **Use the back of the exam pages if necessary**. All mathematical calculations should be written and organized in a logical, neat order. Double-check all your answers where possible. Please express your final answers to **three significant figures**. If necessary, graph paper can be found at the back of this examination.

NOTE: 1. This exam is worth **35% of the final overall grade** in PHM 324. Please note however that the value of all questions total **125** marks.

2. The allotment of marks for each question is indicated beside each question.

3. Potential equations needed to answer the questions are found in the equation booklet. Graph paper is found in the body of the exam. If you require more, you must ask for it.

4. This exam is designed to test your knowledge of pharmacokinetics and possibly even teach you about its use in problem situations. Some issues may be presented which were not specifically dealt with in lectures, but the context of the question should make their meaning clear.

WHERE IT APPEARS NECESSARY,
STATE YOUR ASSUMPTIONS WHEN ANSWERING A QUESTION.
IF SUCH ASSUMPTIONS ARE VALID THEY WILL BE CONSIDERED IN THE GRADING.

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QUESTION 1: (24 marks)

In each of the following questions some information is given. Answer each question based on the DATA provided.

[2] (i) **DATA** V = 50 L
Dose = 150 mg
K = 0.15 hr-1
The concentration at time zero, assuming instantaneous distribution is; **3.00** mg/L
The $AUC_{0-\infty}$ is **20.00** mg*hr/L (2 decimal places)

Initial Concentration = Dose / volume
= 150 mg / 50 L
= 3 mg/L
AUC (0-inf) = Initial Conc / K (Pharmacokinetic method)
= 3.0 mg/L / 0.15 hr-1
= 20 mg*hr/L

[2] (ii) **DATA** $C_{0.5}$ = 9.33 mg/L at time 0.5 hr
$C_{1.0}$ = 8.71 mg/L at time 1.0 hr
The $AUC_{0.5-1.0}$ is **4.52 or 4.53** mg*hr/L (2 decimal places)

Area Calculated by trapezoidal Rule: ((C1+C2)/2) x (t2-t1)
AUC (0.5 – 1.0) = ((9.33 + 8.71) / 2) x (1.0-0.5)
= 9.05 x 0.5
= 4.525 mg *hr/L
or using kinetic method, K = 0.123819 hr-1
and AUC (0.5-1.0) = (9.33/0.1238)-(8.71/0.1238)
= 4.522 mg*hr/L

[2] (iii) **DATA** C_2 = 20 mg/L at time 2 hr
C_4 = 10 mg/L at time 4 hr
K is **0.346** hr-1. (3 decimal places)

Calculation of slope based on rise /run = (log(20)-log(10))/(4-2)
= - 0.15051
K = - 2.303 x –0.15051
= 0.346636 hr-1

using natural logs K = 0.34657 hr

Slope from Excel using logs gives the same answer as rise over run using logs

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[4] (iv) DATA C_4 = 8.0 mg/L at a time of 4 hours
K = 0.1155 hr-1
V = 60 L

The concentration at 0.5 hours is **11.98 (accept 11.98 or 11.99)** mg/L (2 decimal places).

The amount remaining in the body at 8 hours is **302.41** mg (2 decimal places).

Concentration at 0.5 hours based on concentration at 4 hr & k; C0.5 = C4 e(kt)
= 8 e(0.1155 x 3.5)
= 11.985 mg/L

Concentration at 8 hours based on concentration at 4 hr & k; C8 = C4 e(-kt)
= 8 e(-.1155 x 4)
= 5.0401 mg/L

Amount remaining in the body at 8 hours = [ ] @ 8 hr x Vol (l)
= 5.0401 x 60 L
= 302.41 mg

2 marks for each correct answer

[4] (v) DATA

Time (hr)	Plasma Concentration (mg/L)	Urine Collection Period (Start – Stop)	Excretion Rate (mg/hr)
1	16.8		
2	14.1		
4	10.0	0 – 4 hours	12.5
6	7.0		
8	5.0	4 - 8 hours	8.75

The renal clearance is **accept anything between 0.52 and 1.25** L/hr. (2 decimal places)

Renal Clearance is the slope of an excretion rate vs. mid-point plasma concentration, but data does not agree across time points.
Excretion rate of 12.5 mg/hr for 0 – 4 hr interval, uses the 2 hr conc. of 14.1 mg/L: Cl(r)= 0.886 L/hr
Excretion rate of 8.75 mg/hr for 4 – 8 hr interval, uses the 6 hr conc. of 7.0 mg/L; Cl(r) = 1.25 L/hr
Excretion rate based on slope between 2 hr mid point and 6 hr mid point is; Cl(r) = 0.528 L/hr

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[2] (vi) DATA ke = 0.06 hr-1
kme = 1.5 hr-1
K = 0.08 hr-1
km = 0.01 hr-1

The metabolite will have a terminal phase half-life of; **8.66** hr.

Choice of rate limiting exponentials in a metabolite profile is limited to kme and K. Of these exponentials, the smallest value is determined by K at 0.08 hr-1. Half-life is then based on:

Half-life = 0.693/ K
= 0.693/.08
= 8.66 hr

[2] (vii) DATA ke = 0.06 hr-1
kme = 1.5 hr-1
ka = 0.08 hr-1
km = 0.01 hr-1

The Tmax is for the parent compound is **13.35** hr.

Assume K = ke+km and assume knr, is zero
K = 0.06 + 0.01
= 0.07 hr-1
Equation for Tmax is: Tmax = ln(ka/K)/ (ka-K)
= ln(0.08/0.07)/0.08-0.07)
= 13.35 hr

[2] (viii) DATA ke = 0.06 hr-1
kme = 1.5 hr-1
ka = 0.08 hr-1
km = 0.03 hr-1

With parent compound being metabolized and excreted into the urine, the parent compound will have a terminal phase half-life of: **8.66** hr.

Assume K = ke+km and assume knr, is zero
K = 0.06 + 0.03
= 0.09 hr-1

Choice of rate limiting exponentials in a parent compound profile is limited to ka and K. Of these exponentials, the smallest value is determined by ka at 0.08 hr-1. Half-life is then based on:

Half-life = 0.693/ ka
= 0.693/.08
= 8.66 hr

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[4] (ix) DATA Dose = 200 mg
Cmax = 8.58 mg/L
Tmax = 3.8 hr
AUC = 93.154 mg*hr/L
F = 0.8
K = 0.1155 hr-1

The volume of distribution for the parent compound is: _____L.

There may be other approaches to this question but it is most easily answered through clearance Cl = K x V and Cl = Dose/AUC, or in this case Cl = FDose/AUC. Therefore; KV = FDose/AUC or FDose / KAUC

= FDose / K x AUC
= 0.8*200 mg / 0.1155 hr-1 x 93.154 mg*hr/L
= 14.87 L

Accept 14.87 – 14.9 L for FULL marks

QUESTION 2. (18 Marks)

A patient is given an IV bolus dose of 100-mg of ciprofloxacin. Blood samples are drawn and the plasma concentrations are determined and are shown below.

Time (hr)	Concentration (mg/L)
0	
2	7.07
4	5.00
6	3.53

[2] (i) What is K (hr-1)? _____ hr-1

There are a variety of ways this can be calculated ranging from inspection (K=0.17325 hr-1) to rise over run using common logs or natural logs. Accept answers from 0.1732 to 0.1741 hr-1. With 3 sig fig this would range from 0.173 to 0.174 hr-1.

[2] (ii) What is the half-life (hr)? _____ hr

There are a variety of ways this can be calculated from the K value and this gives rise to answers ranging from inspection (T½ = 4 hr) to rise over run using common logs or natural logs. Accept answers from T½ = 3.98 to 4 hr. With rounding from K, allow 3.97 to 4.01 hr.

[2] (iii) Calculate the volume of distribution (L). _____ L

There are a variety of ways this can be calculated based on K and the concentration used for back extrapolation. These choices result in a variety of estimates of the initial concentration ranging from 9.979 to 10.033 mg/L (maintaining all decimal places during calculation) to 9.9928 L to 10.0128 mg/L if K is truncated at 3 decimal places. This results in estimates of the volume ranging from 9.967 L to 10.020 L. Accept answers from 9.9 to 10.1 L.

[2] (iv) What is the $AUC_{0-\infty}$ (mg*hr/L)? _____ mg*hr/L

The rule stated in class is that with IV bolus dosing AUC was to be calculated using the pharmacokinetic method; initial concentration / K. With potentially varying k values answers can range from 57.54 mg*hr/L to 57.76 mg*hr/L. Accept answers from 57.4 mg*hr/L to 57.9 mg*hr/L. **FULL MARKS**.

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Even though it was repeated several times in class that trapezoidal rule should not be used in this case, an answer which will slightly over-estimate AUC. With variations in K and volume these answers can range from 57.97 to 58.067 mg*hr/L. Accept answers from 57.95 to 58.2 mg*hr/L **(1.5 Marks).**

[2] (v) Calculate Total Body Clearance (L/hr). _____ L/hr

Clearance in this case is calculated based on Dose / AUC. There are a variety of answers based on the method of calculation of K, and even allowing trapezoidal rule as a method of estimating AUC. These choices result in a variety of estimates of the initial concentration ranging from 1.723 L/hr to 1.725 L/hr . Accept answers, for full marks from 1.70 to 1.74 L/hr.

[2] (vi) What is the concentration at 1 hour? _____ mg/L

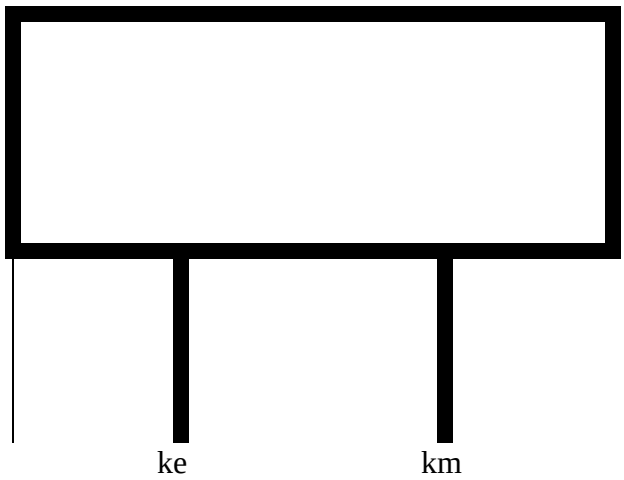
There are a variety of ways this can be calculated based on K and the concentration used for back extrapolation. These choices result in a variety of estimates of the concentration at one hour from 8.3838 to 8.4258 mg/L Accept answers for FULL MARKS from 8.30 to 8.50 mg/L.

[2] (vii) At 9 hours, how much drug (mg) remains in the body? _____ mg

Again there are a variety of ways this can be calculated based on K and the concentration used for back extrapolation. These choices result in a variety of estimates of the concentration at 9 hour from 2.0900 to 2.1061 mg/L Together with the accepted range for volume calculated in (iii) ranging from 9.9 to 10.1L, amount remaining will vary between 20.69 and 21.27. Accept answers for FULL MARKS from 20.6 to 21.5 mg/L.

[4] (viii) Draw a model labeled with the rate constants (ke, km) and their values with units of hr-1.

A value allowing determination of rate constants was removed in final exam assembly, so values could not be calculated. Accept just a diagram showing a 1-compartment model with ke and km as rate constants.



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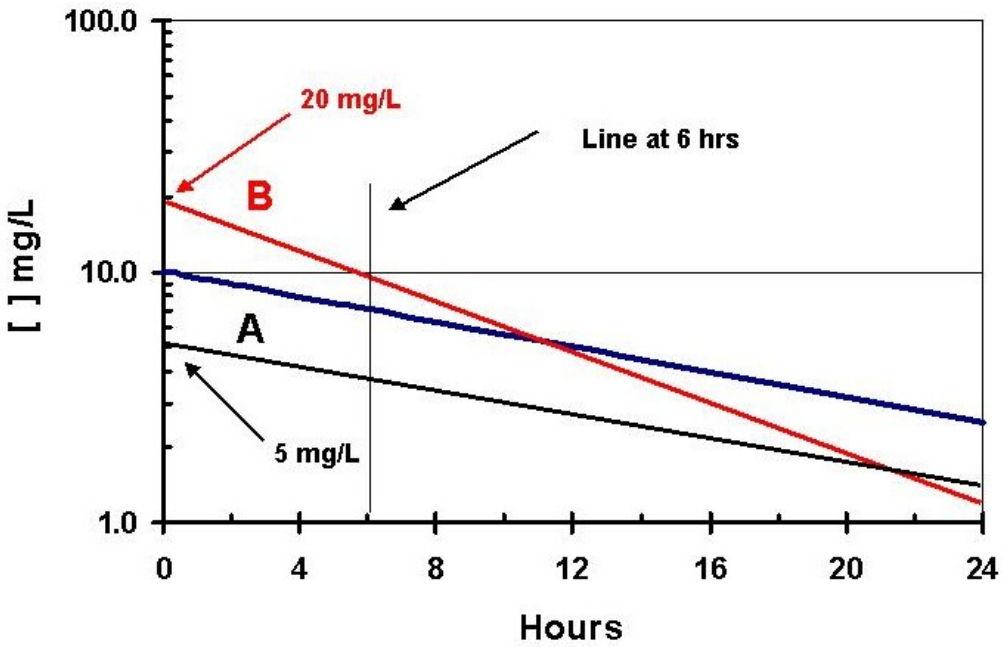
QUESTION 3 (4 Marks)

Following a 400 mg IV dose of moxifloxacin to Mr BB, the following serum concentrations are observed. The graph below plots these concentrations. On the same graph draw 2 more lines clearly identified as line **A** and **B**.

Time (hr)	Concentration (mg/L)
0	10.00
4	7.94
12	5.00
24	2.50



[2] (i) **Line A** will represent a moxifloxacin profile where the distribution space is twice that observed in Mr. BB but the half-life is identical to that observed in Mr. BB.

Line A is the black (lower line in the graph above). It will have a time zero concentration of 5 mg/L (1 mark) and a slope parallel to the middle (blue) line. To get the mark demonstrating similar half-life, a parallel the line should either be parallel (looks close) or a statement should indicate that the line is parallel. Exact Time – Concentrations will be: 0:5; 12:2.5; 24:1.25.

[2] (ii) **Line B** will represent a moxifloxacin profile where the distribution space is half that observed in Mr. BB but the clearance is identical to that observed in Mr. BB.

Line B is the RED (upper line in the graph above). It will have a time zero concentration of 20 mg/L (1 mark). Since clearance is identical but volume is half: [Cl = (0.5V)(2K) and T½ = 0.693/2K and 0.5T½ = 0.693/K], the T½ must be half that observed in the given (blue) line. This is a half-life of 6 hours, but it is not necessary to state this. To get the mark demonstrating that the half-life is half that seen in the blue line, the line should pass through a point, 1 half-life later, with a concentration of 10 mg/L at 6 hours. The line should either be marked as passing through this point, or look like it does. Exact Time – Concentrations will be: 12:5; 24:1.25.

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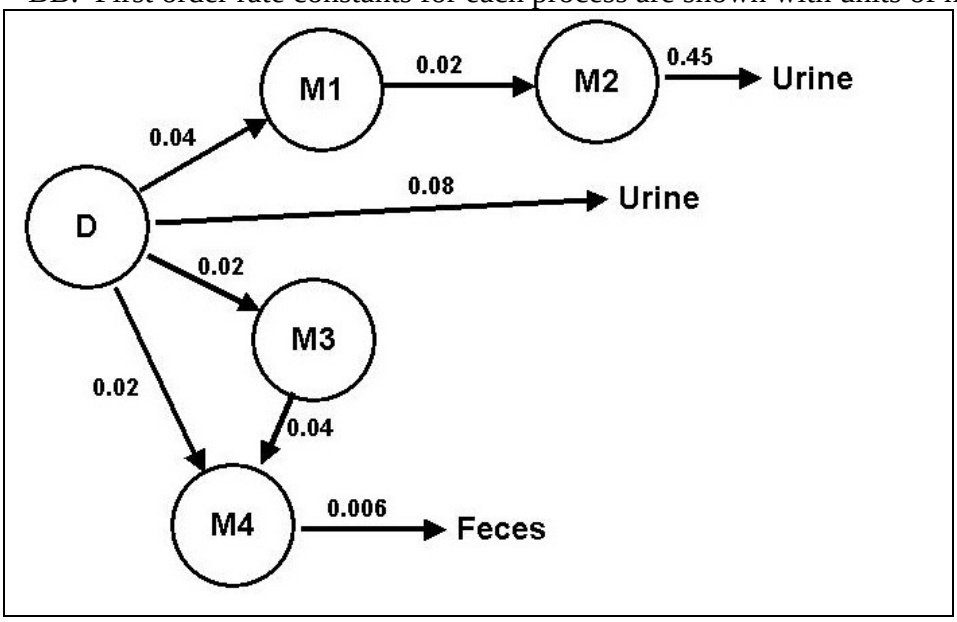
QUESTION 4 (16 Marks)

A new drug (D) was observed to be excreted unchanged into the urine and 4 different metabolites were observed in serum/urine or feces following a 100-millimole IV dose to Mr. BB. First order rate constants for each process are shown with units of hr-1.



[10] (i) Complete the table below based on this metabolic scheme.

Compound	Total Amount Excreted	Excretion Location
D	0.08/ (0.02+0.02+0.08+0.04) = 0.50 = 50% 100 millimoles x 50% = **50 millimoles**	Urine
M1	Zero	Not excreted
M2	0.04/ (0.02+0.02+0.08+0.04) = 0.25 = 25% 100 millimoles x 25% = **25 millimoles**	Urine
M3	Zero	Not excreted
M4	0.02+0.02 / (0.02+0.02+0.08+0.04) = 0.25 = 25% 100 millimoles x 25% = **25 millimoles**	Feces

[2] (ii) The Half-life of D in this patient is: _____ hr

K is the sum of individual rate constants; K = 0.02+0.02+0.08+0.04 = 0.16 hr-1

T½ = 0.693/ K
= 0.693 /0.16 hr-1
= 4.33 hr.

[2] (iii) The terminal elimination half-life of M4 in this patient: _____ hr.

Rate limiting step is elimination of M4 into the urine (kme).
Since kme has a value of 0.006 hr-1, T½ = 0.693/ K
= 0.693 /0.006 hr-1
= 115.50 hr.
Accept 115 hr (3 sig figs).

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[2] (iv) What proportion of D is excreted unchanged into the urine? _____%
The rate constant (ke) which results in D being excreted unchanged into the urine has avalue of 0.08 $hr^{-1.}$
K is the sum of individual rate constants; K = 0.02+0.02+0.08+0.04 = 0.16 hr^{-1}
The proportion excreted unchanged into the urine is:
0.08/ (0.02+0.02+0.08+0.04) = 0.50 = 50%

QUESTION 5 (22 marks)

200-mg of ketoconazole, an antifungal agent of the imidazole class, was administered to eight healthy volunteers on 4 separate occasions. Each dose was separated by 1 week. The four doses were;

(i) 200-mg administered by rapid IV bolus,
(ii) 200 mg administered orally with 250 mL of water following an overnight fast, 200 mg administered orally with 250 mL of water following an overnight fast;
(iii) 200 mg administered orally with 250 mL of water, 30 minutes after ingestion of a standard breakfast following an overnight fast; and
(iv) 200 mg administered orally with 250 mL of a cola beverage, following an overnight fast.

Blood samples were drawn over 24 hours and the serum itraconazole concentration determined. Representative pharmacokinetic parameters for each dose are provided in the table below. You may assume a 1-compartment model with first order elimination for all doses and first order absorption for all oral doses.

Average pharmacokinetic results following 200-mg doses of itraconazole.

	200-mg IV	**200-mg oral Capsule – Fasting with 250 mL water**	**200-mg oral Capsule – Standard Meal**	**200-mg oral Capsule – Fasting with 250 mL Cola**
Cmax (mg/L)	13.33	3.68	2.54	6.23
Tmax (hr)	0	2.68	3.75	1.6
Half-life (hr)	2	2	2	2
$AUC_{0-\infty}$ (mg*hr/L)	38.48	27.57	27.40	31.55
ka (hr-1)	na	0.4	0.2	1

[2] (i) The total clearance of itraconazole is _____ L/hr. (do not assume F=1)
This may be calculated from any route and if done correctly, the answer will be the same in all cases.
This may be calculated using any route of administration although it is easiest from the IV dose where F is known to be 1. Clearance should be calculated using the formula of FDose / AUC. Accept answers from 5.19 to 5.20 L/hr.

	200-mg IV	**200-mg oral Capsule – Fasting with 250 mL water**	**200-mg oral Capsule – Standard Meal**	**200-mg oral Capsule – Fasting with 250 mL Cola**
Dose (mg)	200	200	200	200
$AUC_{0-\infty}$ (mg*hr/L)	38.48	27.57	27.40	31.55
F		0.7165	0.7121	0.8199
Clearance (L/hr)	**5.1975**	**5.1975**	**5.1975**	**5.1975**

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[3] (ii) The absolute bioavailability (%) of itraconazole when administered with 250 mL of **water** is: _____%

This may be calculated by calculating the ratio of observed $AUC_{0-\infty}$ for the oral Fasting with 250 mL of water with the observed $AUC_{0-\infty}$ for the IV route. Accept answers from 0.716 to 0.717 or as %.

	200-mg IV	**200-mg oral Capsule – Fasting with 250 mL water**	**200-mg oral Capsule – Standard Meal**	**200-mg oral Capsule – Fasting with 250 mL Cola**
Dose (mg)	200	200	200	200
$AUC_{0-\infty}$ (mg*hr/L)	38.48	27.57	27.40	31.55
F		**0.7165**	0.7121	0.8199
Clearance (L/hr)	5.1975	5.1975	5.1975	5.1975

[3] (iii) The absolute bioavailability (%) of itraconzole when administered with 250 mL of **COLA** is: _____%

This may be calculated by calculating the ratio of observed $AUC_{0-\infty}$ for the oral Fasting with 250 mL of COLA with the observed $AUC_{0-\infty}$ for the IV route. Accept answers from 0.81 to 0.82 or as %.

	200-mg IV	**200-mg oral Capsule – Fasting with 250 mL water**	**200-mg oral Capsule – Standard Meal**	**200-mg oral Capsule – Fasting with 250 mL Cola**
Dose (mg)	200	200	200	200
$AUC_{0-\infty}$ (mg*hr/L)	38.48	27.57	27.40	31.55
F		0.7165	0.7121	**0.8199**
Clearance (L/hr)	5.1975	5.1975	5.1975	5.1975

[3] (iv) The absolute bioavailability of itraconazole when administered following a **standard breakfast** is: _____%

This may be calculated by calculating the ratio of observed $AUC_{0-\infty}$ for the oral Standard Meal with the observed $AUC_{0-\infty}$ for the IV route. Accept answers of 0.712 or as %.

	200-mg IV	**200-mg oral Capsule – Fasting with 250 mL water**	**200-mg oral Capsule – Standard Meal**	**200-mg oral Capsule – Fasting with 250 mL Cola**
Dose (mg)	200	200	200	200
$AUC_{0-\infty}$ (mg*hr/L)	38.48	27.57	27.40	31.55
F		0.7165	**0.7121**	0.8199
Clearance (L/hr)	5.1975	5.1975	5.1975	5.1975

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[3] (v) The impact of food (standard breakfast - Test) on bioavailability relative to administration with 250 mL of water is: _____%

This may be calculated by calculating the ratio of observed $AUC_{0-\infty}$ for the Standard Meal and the $AUC_{0-\infty}$ for the oral Fasting with 250 mL. Accept answers from 0.993 to 0.994 or as % for **FULL MARKS**. Given that this could be inverted, allow an answer of 1.0062 or 1.01, for 2 marks.

Also allow the answer expressed as a difference in bioavailability (71.65 – 71.21 %) expressed as either an absolute difference (as a percent: 0.44 %)Accept 0.4 to 0.44%; or in relative terms (0.44/71.65 = 0.612). If you used rounded figures (0.4/ 71.6 = 0.562) , which will also include answers using 71.21 as the denominator.

	200-mg IV	200-mg oral Capsule – Fasting with 250 mL water	200-mg oral Capsule – Standard Meal	200-mg oral Capsule – Fasting with 250 mL Cola
Dose (mg)	200	200	200	200
$AUC_{0-\infty}$ (mg*hr/L)	38.48	27.57	27.40	31.55
F		**0.7165**	**0.7121**	0.8199
F- Relative to Fasting with Water		1.0000	**0.9938**	1.1444

[2] (vi) The terminal half-life following the oral dose administered with 250 mL of water is : _____ hr.

Average pharmacokinetic results following 200-mg doses of itraconazole.

	200-mg IV	200-mg oral Capsule – Fasting with 250 mL water	200-mg oral Capsule – Standard Meal	200-mg oral Capsule – Fasting with 250 mL Cola
Cmax (mg/L)	13.33	3.68	2.54	6.23
Tmax (hr)	0	2.68	3.75	1.6
Half-life (hr)	2	**2**	2	2
$AUC_{0-\infty}$ (mg*hr/L)	38.48	27.57	27.40	31.55
ka (hr-1)	na	**0.4**	0.2	1

The half-life of itraconazole is 2 hours. Route of administration will not change that, although it could change the apparent half-life or terminal phase half-life. The K value associated with a 2 hr half-life is:

$K = 0.693/ T½$
$= 0.693/ 2$
$= 0.3465$ hr-1

Since this is smaller than the absorption rate constant (ka = 0.4hr-1), the terminal elimination half-life is associated with K and the value for the rate constant is 0.3465 hr-1 and this is equivalent to a 2 hr half-life.

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[2] (vii) The terminal half-life following the oral dose administered 30minutes after a standard breakfast is: _____ hr.

Average pharmacokinetic results following 200-mg doses of itraconazole.

	200-mg IV	200-mg oral Capsule – Fasting with 250 mL water	200-mg oral Capsule – Standard Meal	200-mg oral Capsule – Fasting with 250 mL Cola
Cmax (mg/L)	13.33	3.68	2.54	6.23
Tmax (hr)	0	2.68	3.75	1.6
Half-life (hr)	2	2	2	2
$AUC_{0-\infty}$ (mg*hr/L)	38.48	27.57	27.40	31.55
ka (hr-1)	na	0.4	0.2	1

The half-life of itraconazole is 2 hours. Route of administration will not change that, although it could change the apparent half-life or terminal phase half-life. The K value associated with a 2 hr half-life is:

K = 0.693/ T½
= 0.693/ 2
= 0.3465 hr-1

The absorption rate constant (ka) is 0.2hr-1. Since this value is smaller than 0.3465 hr-1, the terminal elimination half-life is associated with ka and the value for the rate constant is 0.2 hr-1. Therefore, the half-life is:

T½ = 0.693/ ka
= 0.693/ 0.2
= 3.465 hr

[2] (viii) Relative to an itraconazole dose administered with 250 mL of water, explain the effect on the rate and extend of itraconazole absorption when it is administered with a cola beverage.

Compared to itraconazole administered on an empty stomach with water, administration of itraconazole with a cola beverage increases the extent of absorption (Ratio AUC = 1.1444) by ~14% and increases the rate of absorption (ka increases from 0.4 to 1.0 hr-1). This increasing rate also results in an earlier Tmax (Tmax moves from 2.6 hr to 1.6 hrs.).

1 mark for “increases extent”
1 mark for “increases rate”

[2] (ix) Based on these results, if you were writing the CPS monograph for this compound explain the effect of food on the rate and extent of itraconazole absorption.

Compared to itraconazole administered on an empty stomach with water, administration of itraconazole with a standard breakfast has no effect of the extent of absorption (Ratio AUC = 0.9938) but absorption is slowed as the rate of absorption (ka) decreases from 0.4 to 0.2 hr-1). This reduction in rate results in a later Tmax (Tmax moves from 2.6 hr to 3.75 hrs.).

1 mark for “no change in extent” or equivalent
1 mark for “reduces rate” or equivalent

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QUESTION 6 (12 Marks)

A large 800-mg oral dose of celecoxib (Celebrex®)is given to a patient. Blood samples are drawn and the plasma concentrations are determined and are shown below.

Time (hr)	Concentration (mg/L)
0	0.00
0.25	0.68
0.5	1.24
1	2.10
1.5	2.67
2	3.02
3	3.28
4	3.19
6	2.60
12	0.98
18	0.32
24	0.105

[2] (i) On the next page, a piece of 2 – cycle semi-log paper can be found. Graph data on this paper. Label each axis appropriately.

The Graph must have a properly labeled and constructed x and y-axis (1/2 mark each) and all points plotted appropriately (1 mark)

[2] (ii) ON THE GRAPH, using the last 3 points, back extrapolate the terminal phase and estimate a concentration at time zero (intercept). Clearly mark the intercept and print the estimated time zero concentration near the intercept, ON THE GRAPH.

When completed mathematically there are a variety of ways to determine the intercept, based on selection of points. Using only concentrations at 12, 18 and 24 hours, the intercept can be shown to range from 9.05 to 9.25 mg/L. When completed graphically an intercept of between 9.2 and 9.3 mg/L can be obtained. Allowing for some deviation, **one mark** will be given for a line the goes through all 3 concentrations at 12, 18 and 24 hrs and **an additional ½ mark** if the continuation of this line intersects the y-axis between 8.7 and 9.8 mg/L and the **final ½ mark** if this observed intercept is properly labeled on the graph.

[2] (iii) Describe, in words, a model that appears to satisfy the concentration-time profile.

Although you have not been shown the second exponential derived through the method of residuals and are therefore, unable to assess if it is a log-linear process, the rounded nature of the concentration-time profile would indicate a first order absorption process. The terminal phase is also log-linear. However, at this point we do not know if the rate-limiting step is absorption or elimination. Furthermore, since there does not appear to be a "nose" of distribution, a model describing the concentration-time profile would be a 1-compartment model with first order oral absorption and first order elimination.

1 mark for 1-Compartment model

1 mark for either first order elimination or first order absorption

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[2] (iv) The terminal phase half-life observed for celecoxib is: _____ hr.

There are a variety of ways that K can be calculated based on the selection of two points in the terminal phase. While the last 2-points represent the safest pair, the graphing step in question (ii) demonstrated that the last three points lie on the line. Using any two of the last 3 points will yield a K value ranging between 0.1857 – 0.1867 value and this gives rise to T½ answers ranging from 3.71 to 3.73 hr. Use of the concentration at 6 hours (which is not in the terminal phase) with any other point from 12, 18 or 24 hrs, produces half-lives ranging from 3.88 to 4.26 hr. Therefore, accept answers from T½ = 3.65 to 3.80 hr.

[2] (v) If you use the method of residuals to determine the value of a second exponential, the value is determined to be 0.50 hr-1. What rate constant(s) could this value be associated with?

Since you have been told that 800-mg was given orally, your choices for potentially rate limiting steps include only ka and K. The terminal phase rate constant was just determined to have a value of 0.186 hr-1. Since we have not been given any information about the half-life of celecoxib following IV administration (in reality these studies have not been completed because of the poor solubility of celecoxib) we do not really know the half-life of celecoxib in this patient. Therefore, the terminal phase could be associated with **either ka or K. (1 mark given for each).** In fact, the CPS reports an "effective" half-life of celecoxib of 11-12 hours and states that "low solubility of the drug prolongs the absorption process…" In constructing the question the celecoxib half-life was changed to eliminate the possibility of prior knowledge of the "effective" half-life impacting on this answer and to improve the sensitivity with which graphical determination of the intercept was completed.

[2] (vi) Given a value of the second rate constant of 0.5 hr-1, what is the actual Tmax for this dose in this patent.

The Equation for Tmax is: $T_{max} = \ln(ka/K)/(ka-K)$

Not knowing if the terminal phase represents ka or K is not important as both of the following two equations will yield the same answer.

$T_{max} = \ln(ka/K)/(ka-K)$ Therefore: $T_{max} = \ln(K/ka)/(K-ka)$

$T_{max} = \ln(ka/K)/(ka-K)$

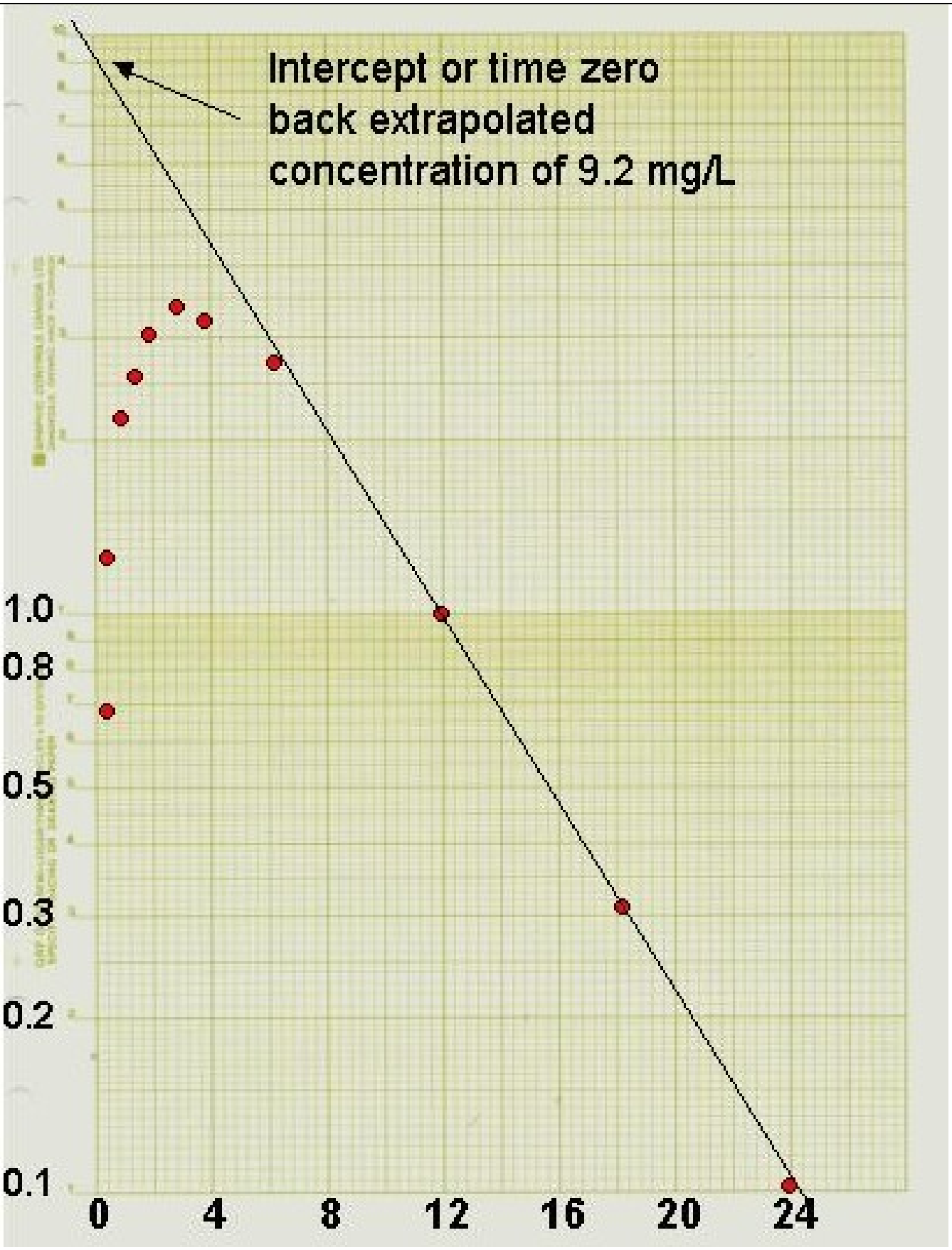
$= \ln(0.5/0.1862)/0.5-0.1862$

$= 3.15$ hr

Ranges in K will produce answers falling between 3.14 and 3.16 hr.

Since use of the concentration at 6 hours with any a concentration from 12, 18 or 24 hours will yield a Tmax of 3.2 hr or greater, **1 mark is given for the process and 1 mark is given for a Tmax answer of 3.13 to 3.16 hr.**

Name : _____
Last Name First name



Name : _____
Last Name First name

QUESTION 7 (6 MARKS)

The hepatic intrinsic clearance of Drug X was determined in early clinical development. Based on the data provided, calculate the required parameters.

Data for Drug X : Q_h = 825 ml/min
CL_{int} = 1420 ml/min
F^{abs} = 0.7
F^{dis} = 1

a) **CL_H = _____ L/hr.**

b) **F_{oral} = _____**

QUESTION 8 (18 MARKS/ 3 each)

A novel antidepressant agent, BLISS is eliminated by intestinal exsorption, renal excretion and hepatic metabolism to 3-OH BLISS. The metabolite 3-OH-BLISS is completely eliminated via renal excretion. Studies in healthy volunteers established the following pharmacokinetic parameters for BLISS based on plasma drug concentrations:

CL_H = 32 L/hr, $CL_{Intestine}$ = 18 L/hr, CL_R = 125 ml/min, Vd = 165 L

Assuming a liver plasma flow rate of 825 ml/min, please calculate the following for BLISS:

i) t½ = _____ hr.

ii) After an IV dose of BLISS and collection of urine for >12 t½,

_____ % of the dose will be recovered in urine as **BLISS**,

_____% of the dose will be recovered as **3-OH-BLISS.**

iii) Hepatic **CL_{int} = _____ L/hr**

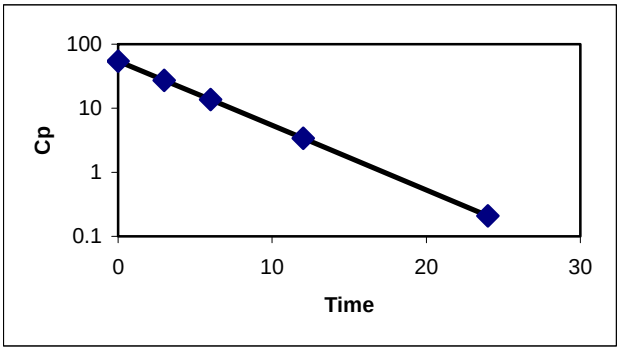
iv) If **liver plasma flow rate is decreased** in patients to 600 ml/min **(**intrinsic enzyme activity not affected); **hepatic ER = _____ .**

v) BLISS is cleared renally by **glomerular filtration** alone, therefore you would expect a **CLr of _____ ml/min** in a 70 year old, 60 kg woman (TBW = IBW) with a serum creatinine of 1.4%

QUESTION 9 (5 MARKS)

On the graphs below, draw **representative lines** depicting the **anticipated change** in plasma concentration versus time curves when enzyme activity is increased (ie. 2 fold enzyme induction). Exact numbers are not needed – draw the general trend line. Use dotted line, colored pen or pencil to depict change.

a) HSR224 (ER = 0.85)



b) GSK002 (ER= 0.15)