Name: _____
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Student Number: Answer Key

[Some answers could have used different approaches]

PHARMACY 324
PHARMACOKINETICS
Term #1 EXAM
December 8, 2003

[Examination time is 3 hours]

This Examination has **17** pages.

PLEASE DO NOT DISASSEMBLE THIS EXAM!
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.** 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**.

ASKING QUESTIONS IS REALLY NOT NECESSARY.

IF YOU ARE UNCERTAIN ABOUT SOMETHING,
MAKE ASSUMPTIONS WHEN ANSWERING A QUESTION.
IF SUCH ASSUMPTIONS ARE VALID THEY WILL BE CONSIDERED IN THE GRADING.

BUDGET YOUR TIME! WATCH THE VALUE OF THE QUESTIONS!

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FACTS AND FIGURES: **[NOTE UNDERLINED PARTS for THIS EXAM]**

Cardiac output (CO) = 85 mL/min/kg total weight
Normal hematocrit (H) = 0.45 unless otherwise noted
Hepatic blood flow (Qh) = 25% of cardiac output
Renal blood flow (Qr) = 25% of cardiac output
Blood volume (L) = 8% of total weight
Body water (L) = 60% of total weight
BSA (m^2) = $(W^{0.425})(H^{0.725})(0.007184)$ [W = kg; H = cm]
% Fat = 90 - 2 (Height - Girth) [Height = inches; Girth = inches]
Lean body mass (LBM) = Total weight - Fat weight
Urine production rate = 0.0143 mL/min/kg total weight [for normal kidneys]
1 in = 2.54 cm

NOTE:
1. This exam is worth **35% of the final overall grade** in PHM 324. Please note however that the value of all questions totals 100 marks.
2. The allotment of marks for each question is indicated beside each question.
3. The available equations, as indicated in class, are found in the supplementary pages. Additional graph paper is found at the back of the exam.
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.*

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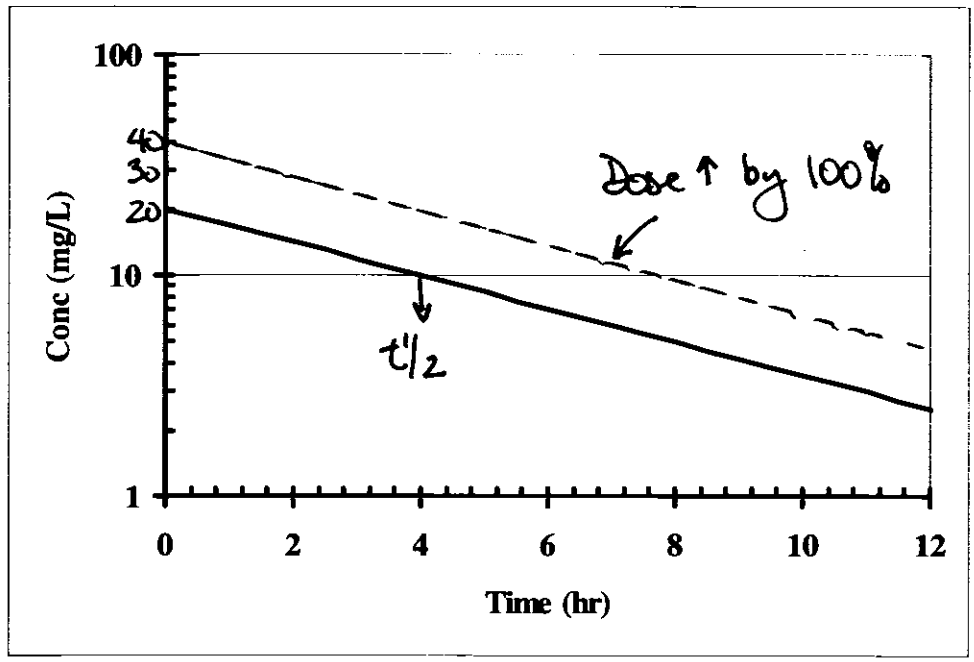
QUESTION 1: (26 marks; the marks are found beside each question)

In each of the following questions, some information is given. Answer the question based on the **DATA or the CHART**. Each **DATA** or **CHART** represents a new independent information source.

[4] a) **CHART**:



[1] i) The half-life is 4 hr. $k = \frac{0.693}{4} = 0.17325\ hr^{-1}$

[1] ii) The mean residence time is 5.77 hr. $MRT = \frac{1}{k}$

[2] iii) Draw a line on the above CHART to show what would be expected if the dose increases by 100%.

[4] b) **DATA**:

IV Dose =	200 mg
k =	0.1155 hr^{-1}
C at 12 hr =	5 mg/L
V1 = Vss	

[2] C° is 20 µg/mL. $C^\circ = \frac{5}{e^{-k(12)}}$

[1] Total AUC is 173 (µg/mL)*hr. $AUC = \frac{20}{0.1155}$

[1] Total clearance is 1.16 L/hr.

$Cl_t = kV_1$

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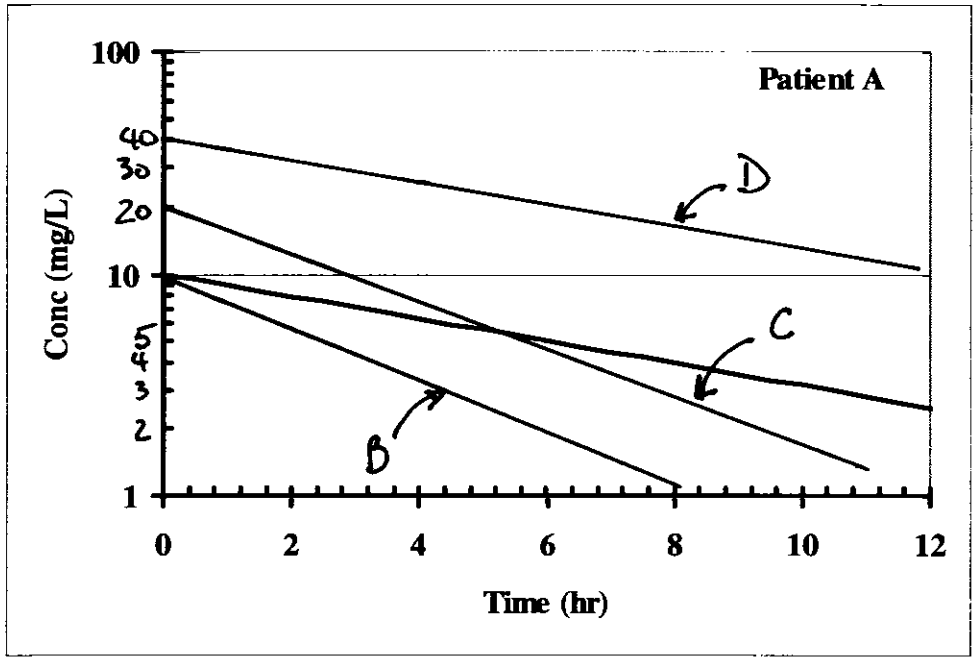
[6] c) **CHART**: Dose for **Patient A** is 600 mg.



All of the following comparisons are against Patient A.

[2] Draw a line on the above CHART for **Patient B** which has the same distribution space but twice the total body clearance. Identify your line for patient B.

[2] Draw a line on the above CHART for **Patient C** which has the same clearance but one-half the distribution space. Identify your line for patient C.

[2] Draw a line on the above CHART for **Patient D** which receives twice the dose, has one-half the distribution space and one-half the total clearance. Identify your line for patient D.

[6] d) **DATA**:

*Blood Data***	
V1 = Vss =	0.5 L/kg
CLh = CLm	
$ER_{hepatic}$ =	0.2
ER_{renal} =	0.05

$\dot{Q}_h$ or $\dot{Q}_r$ = 1.275 L/kg/hr

$Cl_h = 0.2(1.275)$

$Cl_r = 0.05(1.275)$

$Cl_t = 0.25(1.275)$

$fe = \frac{Cl_r}{Cl_t}$

[3] The total body clearance is 0.319 L/kg/hr.

[2] fe = 0.20

[1] Half-life = 1.09 hr

$k = Cl_t / V_1 = 0.31875 / 0.5 = 0.6375$

$t_{1/2} = \frac{0.693}{k}$

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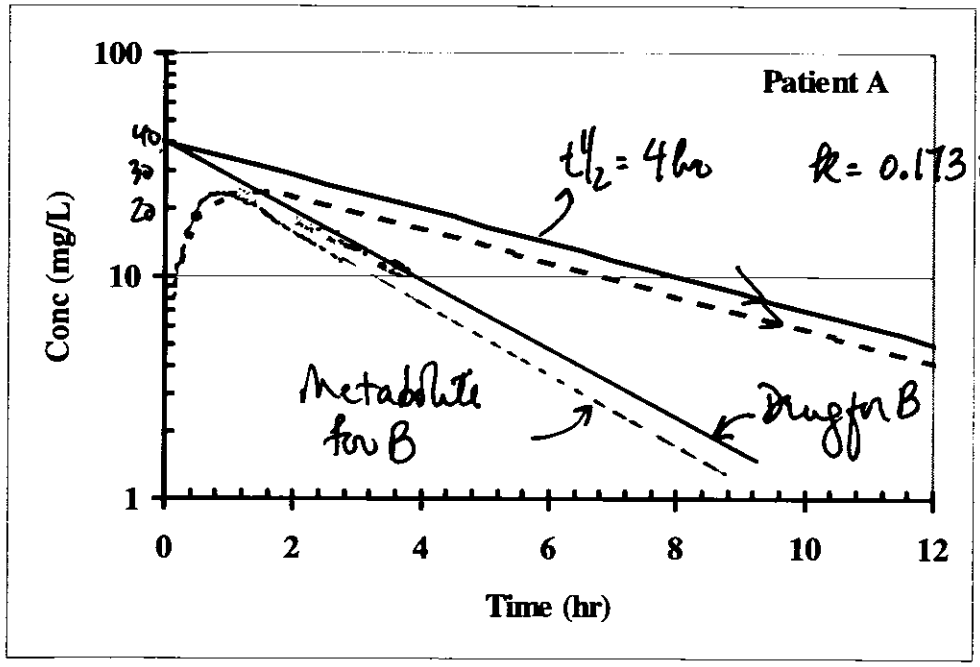
[6] e) **CHART**: Drug and one metabolite for **Patient A**; IV Dose of the drug is 600 mg.



[2] . The rate-limiting elimination constant for the metabolite is 0.173 hr^{-1}.

[4] Draw line(s) on the above CHART for **Patient B** which has:
- the same distribution space for the DRUG
- twice the total body clearance for the DRUG
- has the same fm to the METABOLITE
- the same inherent kinetic properties for the METABOLITE.

Identify any line(s) for patient B.

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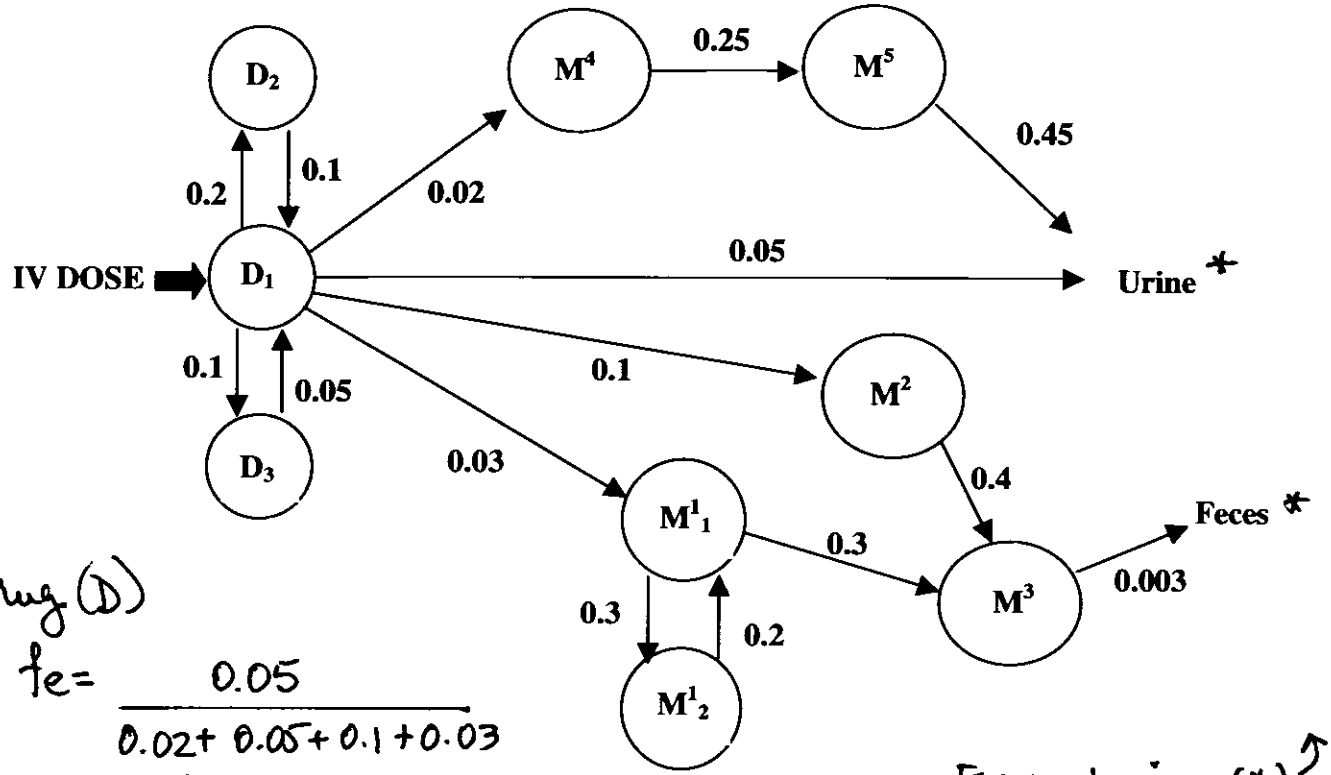
QUESTION 2: (7 marks; the marks are found beside each question)

The following scheme describes the fate of a drug (D) and its metabolites (M^1, M^2 etc.). All constants are in reciprocal hours. All concentrations in the body are in serum. The IV dose of the drug is 2 millimoles.



Drug (D)

$fe = \frac{0.05}{0.02 + 0.05 + 0.1 + 0.03}$

$= \frac{0.05}{0.2} = 0.25$

Excretion = (*) ↑

[5] Complete the following table based on the above scheme.

Compound	Total Amount Excreted (millimoles)	Excretion Location
D	0.25 (2) = 0.5	URINE
M^4	0	Not excreted
M^1	0	Not excreted
M^3	0.65 (2) = 1.3	FECES
M^5	0.1 (2) = 0.2	URINE

[2] The terminal serum half-life of M^3 will be 231 hr.

$\frac{0.693}{0.003}$ ← Smallest constant

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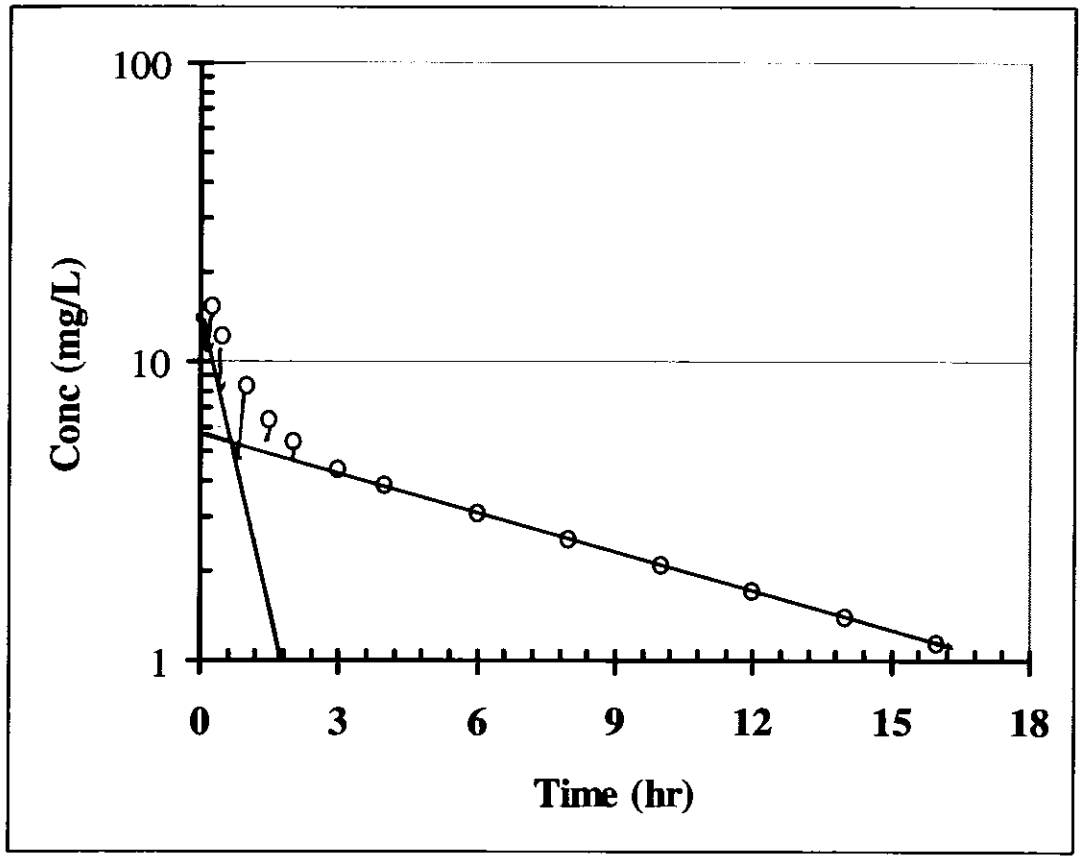
QUESTION 3: (29 marks; the marks are found beside each question)

Decloxacin (DEC; molecular weight = 365) is a new antibiotic used to treat infections, including urinary tract pseudomonas infections. The drug is intended for both intravenous and oral administration. Mr. Martin (80 kg) was given an intravenous bolus dose (5mg/kg) of **DEC**. The following chart shows the serum concentrations versus time following the bolus dose.



Based on the above information, please answer the following questions:

[5] a) The specific equation that best describes the **DEC** serum concentration versus time profile is:

$$C\ (\mu g/mL) = \frac{14.3e^{-1.5t} + 5.7e^{-0.1t}}{\text{[Coefficient(s) in } \mu g/mL;\ \text{constants in } hr^{-1}\ ;\ \text{time in hours]}}$$

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[3] b) The total body clearance for **DEC** in Mr. Martin is 0.0752 L/hr/kg.

$Cl_t = \frac{Dose}{AUC}$

$= \frac{(80kg)(5mg/kg) = 400mg}{66.5(mg/L)hr}$

$= 6.02 L/hr$

$= 6.02/80 = 0.0752 L/hr/kg$

$AUC = A/\alpha + B/\beta$

$= 14.3/1.5 + 5.7/0.1$

$= 66.5 (mg/L)hr$

[3] c) The mean residence time for **DEC** in Mr. Martin is 8.67 hr.

$AUMC = A/\alpha^2 + B/\beta^2$

$= 576.4 (mg/L)hr^2$

$MRT = \frac{AUMC}{AUC}$

$= \frac{576.4}{66.5}$

$= 8.67 hr$

$k_{21} = \frac{A\beta + B\alpha}{A+B} = 0.5 hr^{-1}$

$k_{10} = \alpha\beta/k_{21} = 0.3 hr^{-1}$

$k_{12} = (\alpha+\beta) - (k_{21}+k_{10}) = 0.8 hr^{-1}$

[3] d) The steady state distribution space for **DEC** in Mr. Martin is 0.65 L/kg.

$V_{ss} = V_1(1 + k_{12}/k_{21})$

$= 0.25(1 + 0.8/0.5)$

$= 0.65 L/kg$

or via AUMC & AUC

$V_1 = Dose/A+B$

$= 0.25 L/kg$

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[2] e) The anticipated serum **DEC** concentration in Mr. Martin, 36 hours after the bolus dose, will be 0.156 µg/mL.

$$C = 14.3e^{-1.5(36)} + 5.7e^{-0.1(36)}$$

[2] f) If "fe" for **DEC** in Mr. Martin is 0.25, the **DEC** renal clearance is 1.51 L/hr.

From b), $Cl_t = 6.02$ L/hr

$Cl_r = 0.25(Cl_t)$

$= 1.51$ L/hr

[4] g) If the urinary **DEC** concentration needed to inhibit pseudomonas growth in Mr. Martin is eleven (11) micrograms per mL, the 5 mg/kg IV bolus dose will continue to have an antibiotic effect for 25.1 hr.

① Urine formation rate = 0.0143 mL/min/kg
= 1.144 mL/min for 80 kg
= 68.64 mL/hr

② Urine concentration = 11 µg/mL

③ Urinary excretion rate = 11 (68.64) = 755.04 µg/hr

④ Urinary excretion rate = (Serum cnc)(Renal Clearance)
755.04 = 'x' (1.51 L/hr)
'x' = 500 µg/L or 0.5 µg/mL

⑤ Figure of cvst shows this must be in the β phase
i.e. $0.5 = 5.7e^{-0.1(t)}$
$t = 25.1$ hr

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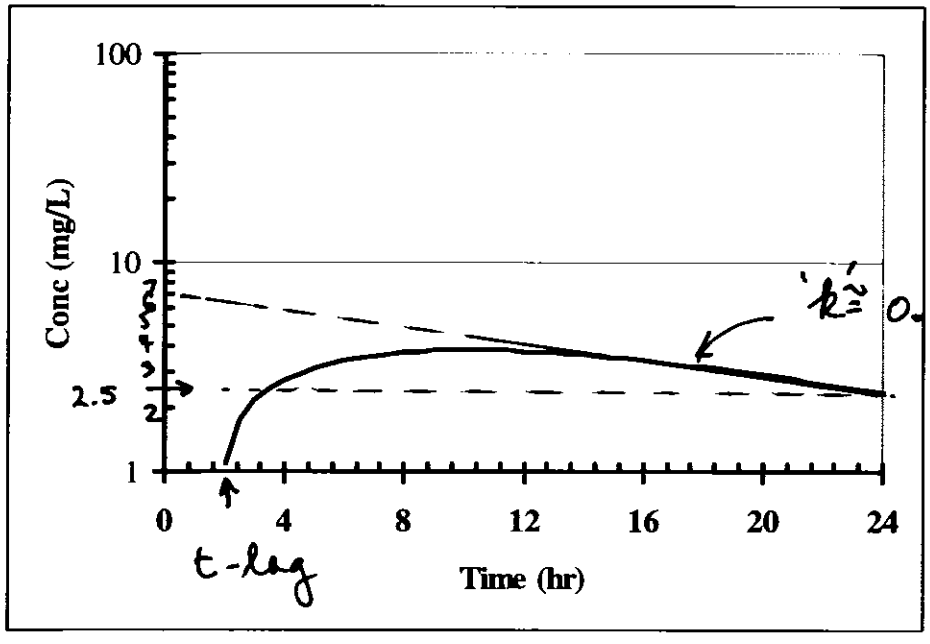
[3] h) At the time point calculated in question "g", 7.52 % of the **DEC** dose in Mr. Martin remains to be eliminated.

At 25.1 hr, AUC left $= \frac{C^{25.1}}{\beta} = \frac{0.5}{0.1} = 5$ (µg/mL) hr

$\therefore$ % remaining $= \left(\frac{AUC_{25.1}^{\infty}}{AUC_{0}^{\infty}}\right)100 = \frac{(5)100}{66.5} = 7.52\%$

[4] i) The following serum **DEC** concentration profile was observed when a 600 mg oral dose of **DEC** was given to Mr. Martin on a separate occasion. In the space below the figure, describe any special pharmacokinetic characteristics of this oral dose.



Special features: (600 mg oral dose)

① The product exhibits a delay in absorption (Time lag) of about 2 hrs.

② The Terminal constant is about 0.043 hr^{-1}. This is smaller than α or β. Therefore, it appears absorption is rate-limiting the elimination process ($k_a \cong 0.043\ hr^{-1}$)

③ The above (#②) explains why a 2-cpt drug (DEC) shows 1-compartment characteristics in oral administration of the 600 mg product

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QUESTION 4: (20 marks; 2.5 marks each)

Prezic™ is a newly marketed antidepressant drug which is eliminated by hepatic metabolism and renal excretion. The following plasma and urine data was obtained following the administration of a **10 mg IV dose** to a 68 kg male subject (45 years old).

PLASMA DATA:

Time	Plasma Concentration (µg/L) Prezic™
0	54.3
3	27.15
6	13.6
12	3.4
24	0.42

Trapezoid AUC

$AUC_0^{24} = 257.2 (\mu g/L)\,hr$

$k = 0.231\ hr^{-1}$

$t_{1/2} = 3\ hr$

$AUC_{24}^{\infty} = \frac{0.42}{0.231} = 1.82$

$AUC_0^{\infty} = 257.2 + 1.82 = 259.0 (\mu g/L)\,hr$

URINE DATA:

Urine Collection Period	Amount Prezic™ in urine (mg)
0-6 hr	0.489
6-12 hr	0.122
12-24 hr	0.031

Ae^{24} 0.642 mg = 642 µg

Part 1: Assuming a liver plasma flow rate of 825 ml/min, please calculate the following for Prezic™. Please show all work, whether calculations or figures to explain your answers. Page 14 offers graph paper and additional space, if this is needed.

a) CL_R = 41.6 **ml/min.**

$Cl_r = Ae^{24} / AUC_0^{24} = \frac{642\ \mu g}{257.2 (\mu g/L)\,hr}$

$= 2.496\ L/hr$

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b) CL_H = 36.1 L/hr.

$Cl_r = 2.496$ L/hr

Cl_t = Dose/AUC = $\frac{10{,}000 \text{ mg}}{259 \text{ kg} \cdot 1 \text{ L/kg/hr}}$

= 38.6 L/hr

$Cl_h = Cl_t - Cl_r$

= 38.6 − 2.5

= 36.1 L/hr

c) $t_{1/2}$ = 3 hr.

via data in plot shown on p. 13.

d) Hepatic ER = 0.729.

$ER = Cl_h / Q_h$; Q_h = 825 mL/min = 49.5 L/hr

= 36.1/49.5 = 0.729

e) CL_{int} = 133 L/hr.

$$Cl_{int} = \frac{Q_h \times Cl_h}{Q_h - Cl_h}$$

$$= \frac{49.5 \times 36.1}{49.5 - 36.1}$$

= 133.3 L/hr

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Part 2: Meals cause a reduction in hepatic plasma flow to approximately 650 ml/min. Estimate the following parameters if Prezic™ is taken with a meal. Assume that neither renal clearance nor intrinsic clearance is affected.

f) CL_H = 30.25 L/hr.

new $\dot{Q}_h$ = 650 mL/min = 39 L/hr

$$Cl_h = \frac{\dot{Q}_h \times Cl_{int}}{Cl_{int} + \dot{Q}_h} = \frac{39 \times 133.3}{133.3 + 39} = 30.17 \text{ L/hr}$$

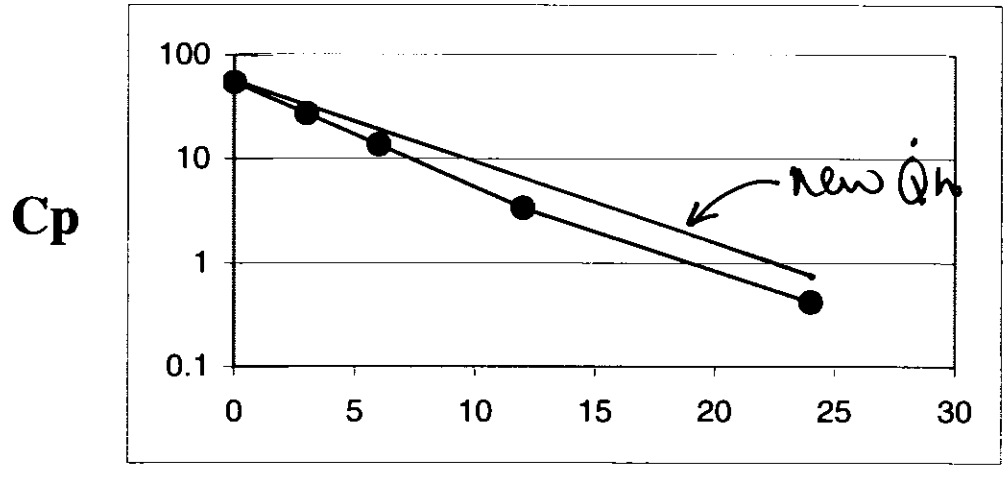
g) $t_{1/2}$ = 3.92 hr.

$$V = Dose/C^0 = \frac{10{,}000\ \mu g}{54.3\ \mu g/L} = 184.2\ L$$

new $Cl_t = Cl_r + Cl_h$
= 2.496 + 30.17
= 32.67 L/hr

$$k = Cl_t/V = 32.67/184.2 = 0.177\ hr^{-1} \qquad t_{1/2} = \frac{0.693}{0.177} = 3.92\ hr$$

Part 3: On the graph below, draw a representative line showing the anticipated change in plasma concentration versus time curve when liver blood flow is reduced (exact numbers not required).)



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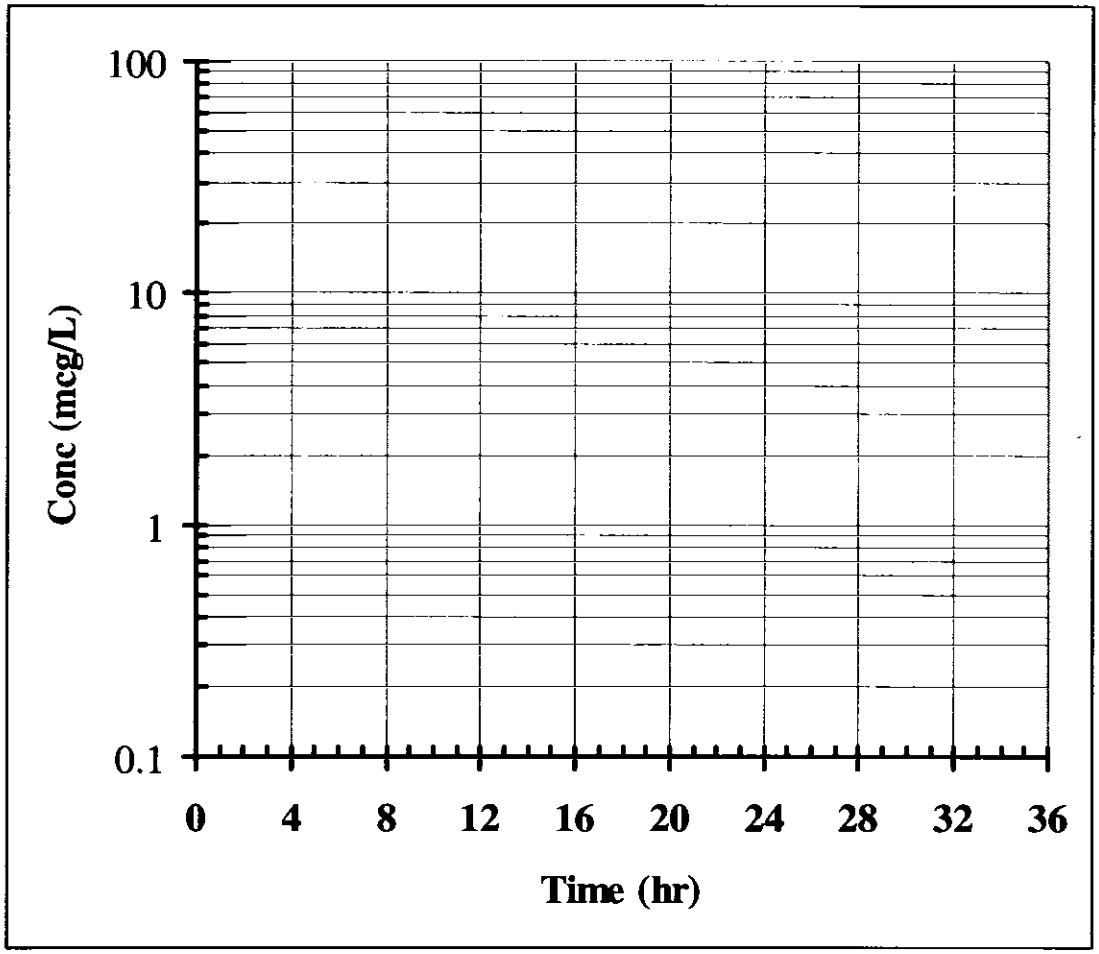

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QUESTION 5: (18 marks; the marks are found beside each question)

Offryth (OF) is an antiarrhythmic agent that has been tested in 12 healthy volunteers whose average total weight was 76 kg. Three doses were given randomly on separate occasions. Whole blood was analyzed.

The following average information was obtained after a 200 mg intravenous bolus dose:

Parameter	Units	Values
V1 = Vss	L/kg	3.9
Total AUC	(µg/L)*hr	6750
Total AUMC	(µg/L)*hr^2	67500
Total **OF** Renally Excreted to 24 hours	mg	130

The following average information was obtained after a 400 mg standard capsule given orally:

Parameter	Units	Values
C^{24}	µg/L	95.4
AUC to 24 hr	(µg/L)*hr	9560
ka	hr^{-1}	0.8
Lag time	hr	0

The following average information was obtained after a 432 mg slow release oral tablet:

Parameter	Units	Values
C^{24}	µg/L	90.0
AUC to 24 hr	(µg/L)*hr	9020
ka	hr^{-1}	0.45
Lag time	hr	1

Please answer the next series of questions based on the above **OF** data.

[4] a) The specific equation that best describes the blood **OF** concentration versus time profile following the IV dose is:

C (µg/L) = $675\, e^{-0.1*t}$

[Coefficient(s) in µg/L; constants in hr^{-1} ; time in hours]

1-cpt. drug

$MRT = \frac{1}{k} = \frac{AUMC}{AUC} = \frac{67500}{6750} = 10\,hr$; $k = 0.1\,hr^{-1}$

$C^0 = \frac{Dose}{V_1} = \frac{200\,mg}{(3.9)(76\,kg)} = 675\,\mu g/L$

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[4] b) The absolute extent of absorption for the standard oral **OF** capsule is 77.9 %.

$$F = \frac{AUC_O}{AUC_{IV}} \cdot \frac{Dose_{IV}}{Dose_O}$$

$$= \frac{10514}{6750} \times \frac{200}{400}$$

$$= 0.779$$

$$AUC_O = 9560 + \frac{C^{24}}{k}$$

$$= 9560 + \frac{95.4}{0.1}$$

$$= 10514$$

[3] c) Although not presented, the expected tmax for the slow release oral tablet is 5.3 hr.

$$t_{max} = \frac{\ln(Ka/k)}{Ka-k} = \frac{\ln(0.45/0.1)}{0.45-0.1}$$

$$= 4.30 \text{ hr}$$

$$t_{lag} = 1 \text{ hr}$$

Total expected $t_{max} = 4.30 + 1$

$$= 5.30 \text{ hr}$$

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[7] d) The anticipated total unchanged **OF** to be excreted into urine after the slow release oral tablet will be 210 mg.

ORAL Tablet

$Ae^{\infty} = fe \cdot F \cdot Dose$

$F = \frac{AUC_0}{AUC_{IV}} \cdot \frac{Dose_{IV}}{Dose_0}$

$AUC_0 = 9020 + \frac{90}{0.1}$

$= 9920$

$= \frac{9920}{6750} \times \frac{200}{432} = 0.68$

For IV data:

$Ae^{24} = 130\ mg.$

$Cl_r = \frac{Ae^{24}}{AUC_0^{24}}$

$= \frac{130\ mg}{6137.7} = 21.18\ L/hr$

$AUC_0^{24} = AUC_0^{\infty} - AUC_{24}^{\infty}$

$= 6750 - \frac{61.23^*}{0.1}$

$= 6137.7$

$Cl_t = \frac{Dose_{IV}}{AUC_{IV}} = \frac{200{,}000\ \mu g}{6750\ (\mu g/L)\ hr} = 29.63\ L/hr$

$fe = \frac{Cl_r}{Cl_t} = 0.715$

$* = \frac{C^{24}}{k}$

$\therefore Ae^{\infty} = (0.715)(0.68)(432) = 210\ mg$