Oral administration

part IV

PK theory lec.12

(Revision of oral administration) تسجيل ع المودل

- ٥٠ دقيقه المحاضرة
- اول ٣٠ دقيقه مراجعة
- باقي المحاضرة حل مسائل امثله

Example 2 $\xrightarrow[\text{دقيقه}]{\text{عند}}$ 30

Example 3 $\xrightarrow[\text{دقيقه}]{\text{عند}}$ 36

Q1 ⟶ 40

$X_0 = 500\ mg$

Example 2

- The presented table gives the plasma drug concentrations that were obtained following the oral administration of 500 mg dose of drug X. Assuming that drug X follows normal pharmacokinetics, determine the following:
  1. Elimination rate constant $K = 0.0883 \times 2.303 = 0.2\ hr^{-1}$
  2. Absorption rate constant $K_a = 0.3814 \times 2.303 = 0.878\ hr^{-1}$
  3. Volume of distribution (normalized for bioavailability)
  4. Bioavailability

بعض مابدو Vd كالها ↓

بدو $\frac{Vd}{F}$

بدو F كالها ↙

Time (hr)	Conc (mg/L)
0.25	3.77
0.5	6.53
0.75	8.49
1.5	11.32
2	11.7
3	10.92
10	2.96
24	0.18
30	0.05

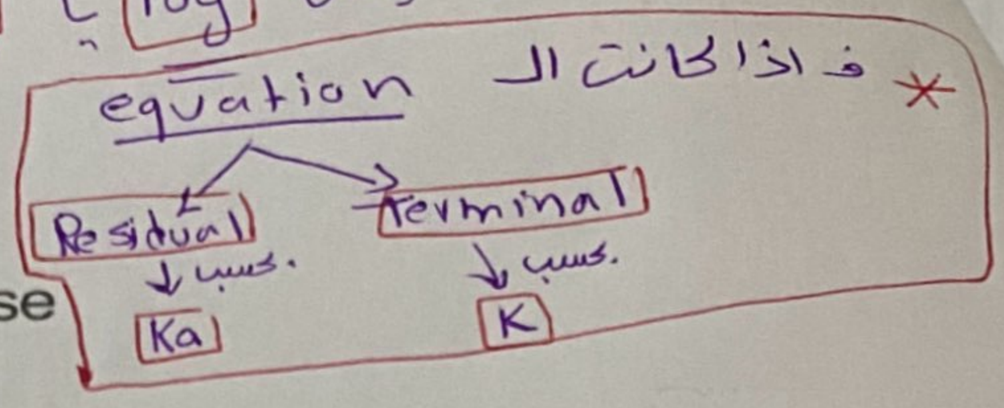
* طلب فيي Elimination rate constant (K) ← stop بدي اطلع من

* طلب فيي Absorption rate constant (Ka) ← stop بدي اطلع من

[بالامتحان حيكون في equation مش رسمة.] * ← وهاد هيني

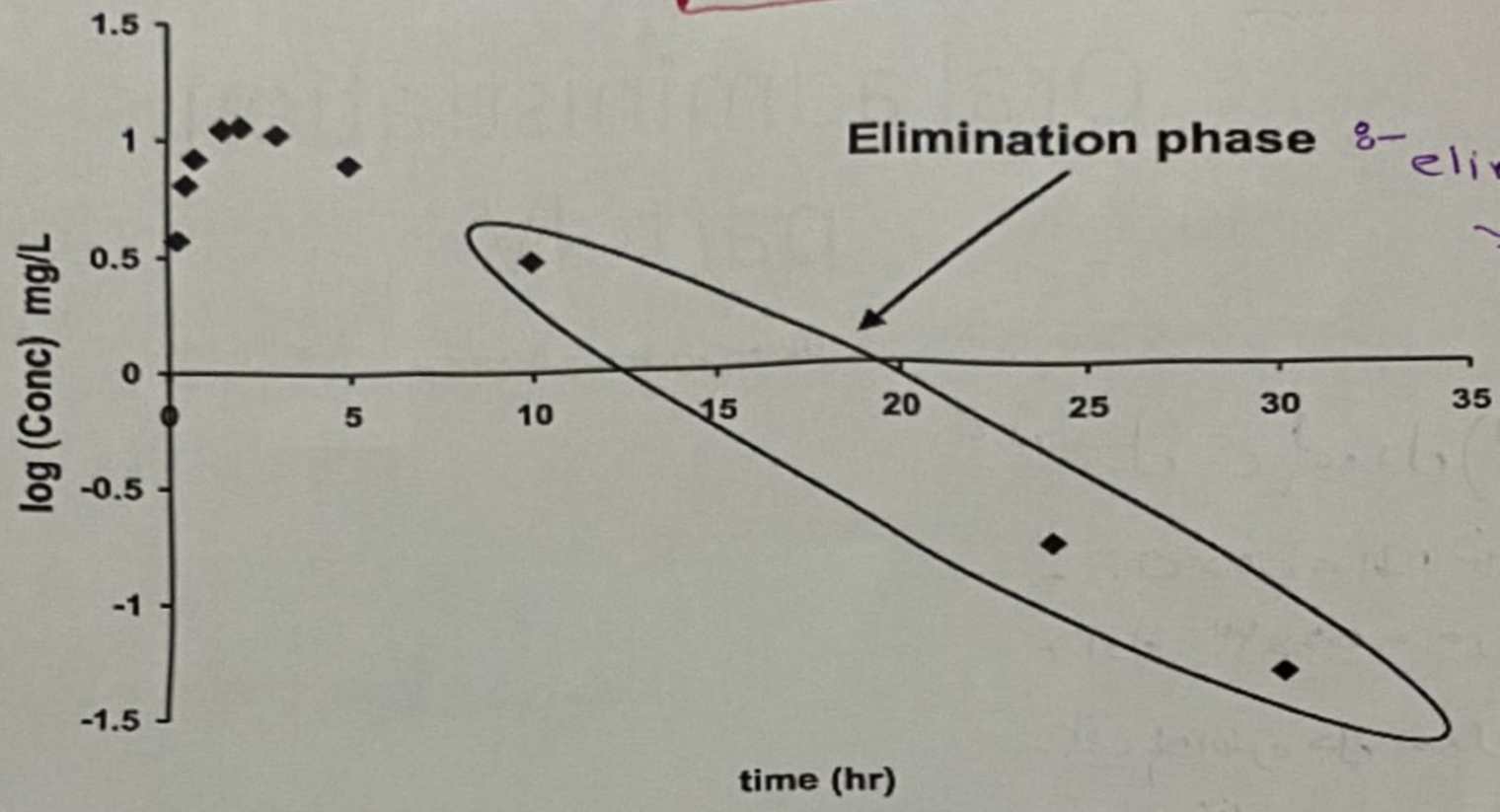
* انه الـ [equation] يا بتكون [ln] يا [log]

* فاذا كانت الـ equation



Example 2:

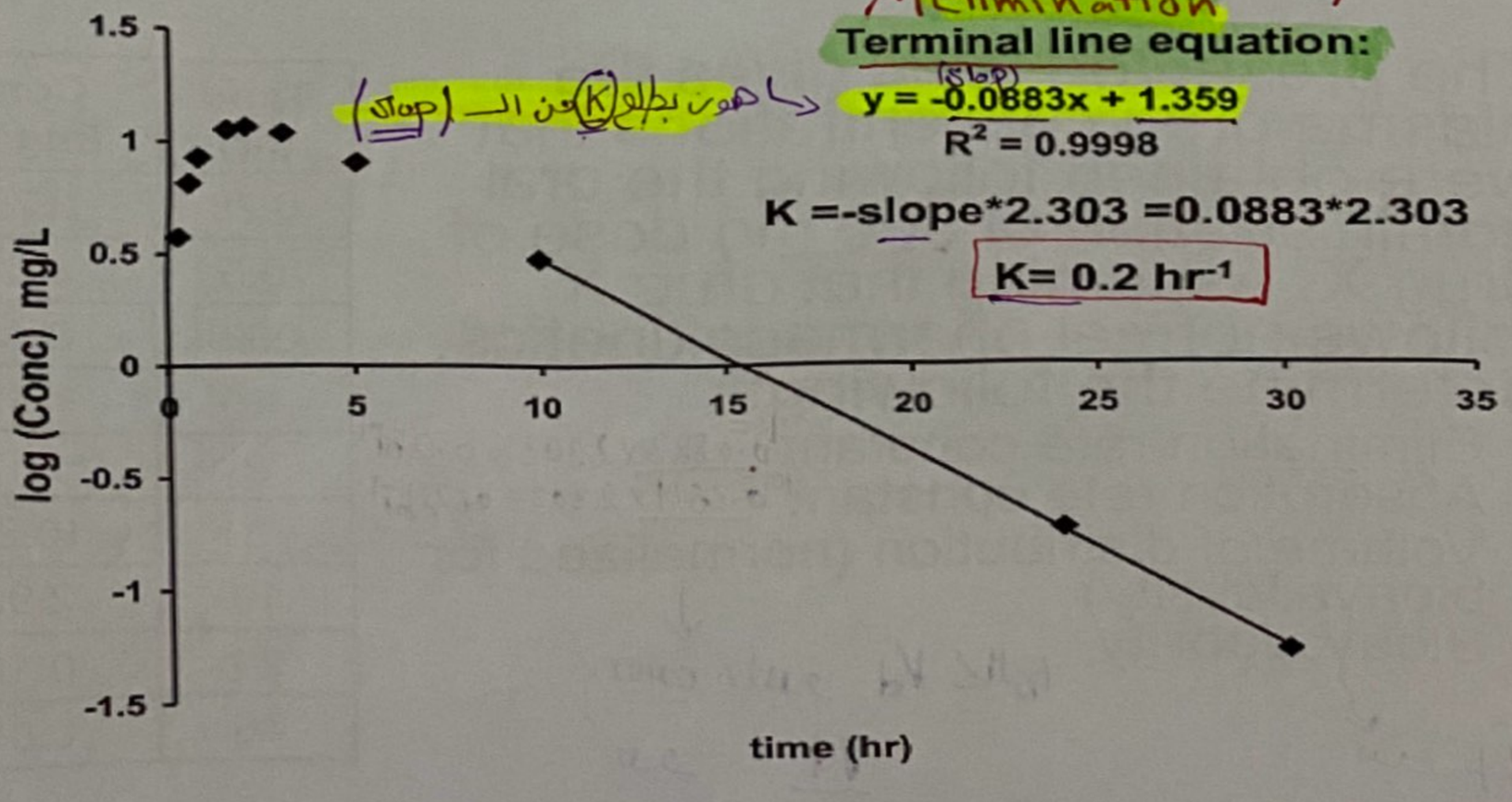
Determine elimination phase



8- elimination phase حلاك ماباكون في عندي absorption.

Example 2:

Determine K



(هوبكون ست elimination)

Terminal line equation: (slop)

y = -0.0883x + 1.359

$R^2 = 0.9998$

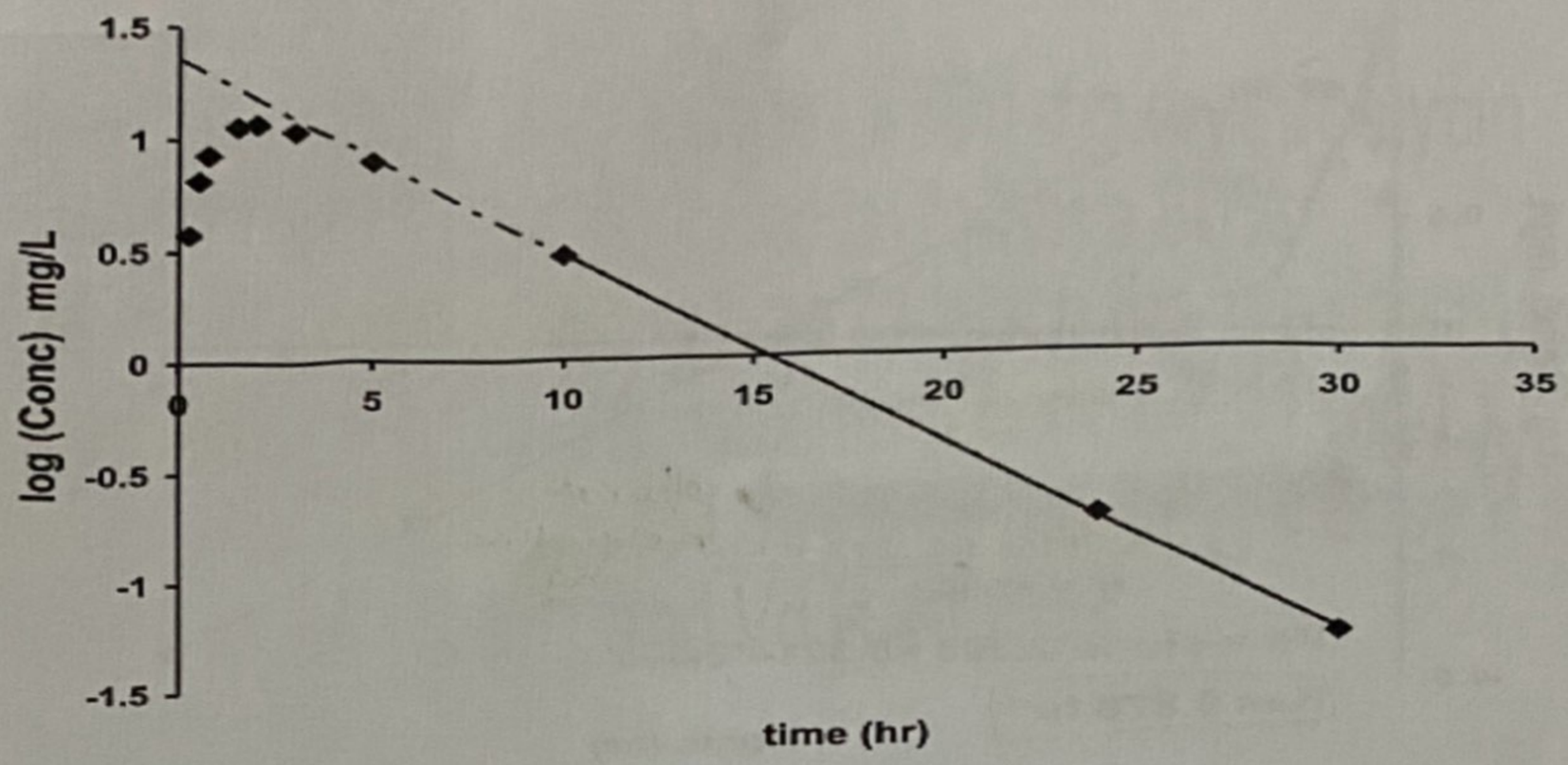
(هون بطلع K عن الـ slop)

K =-slope*2.303 =0.0883*2.303

K= 0.2 hr^{-1}

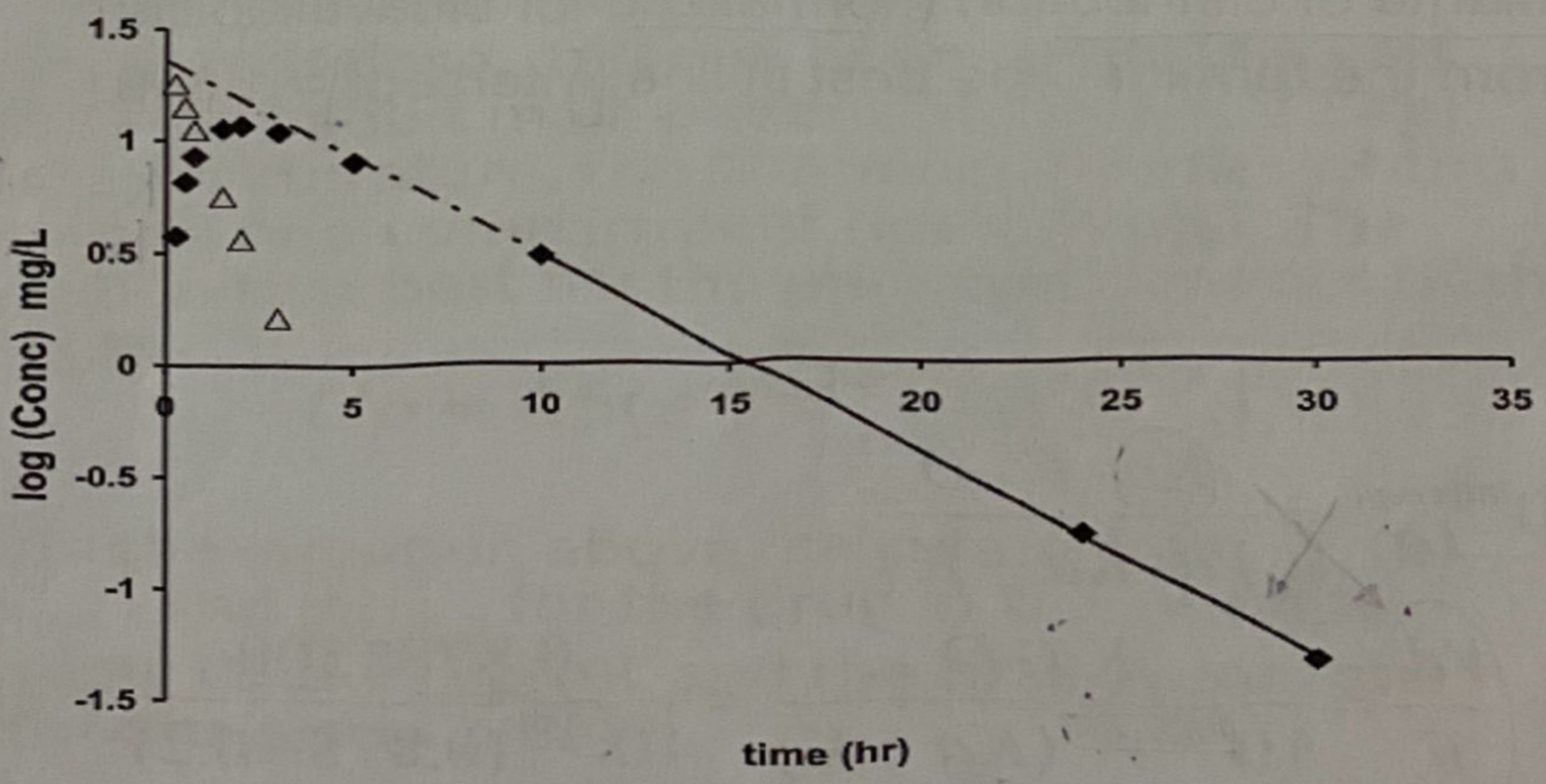
Example 2:

Extrapolate the terminal line to cross the y-axis

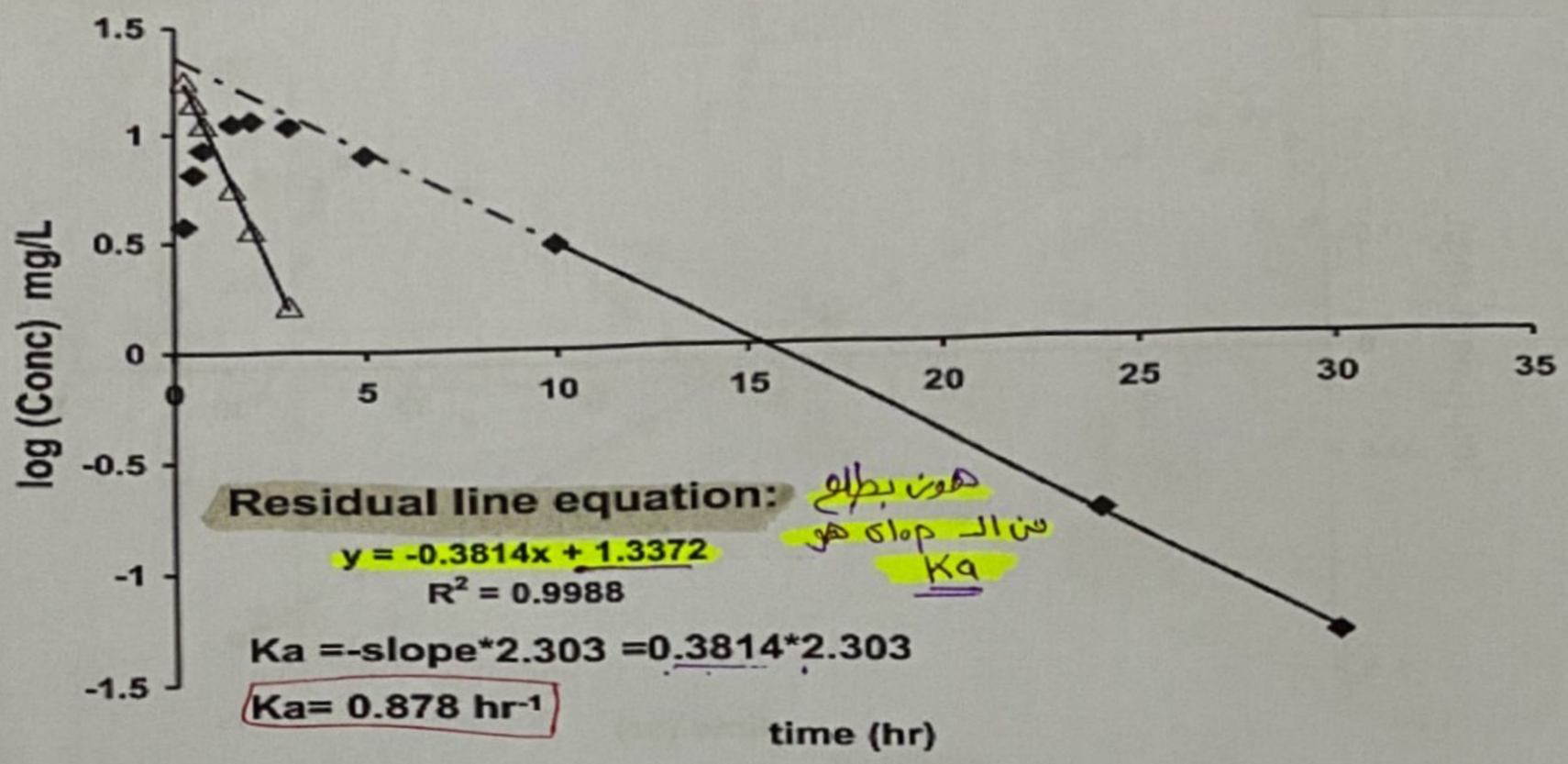


Example 2:

Draw the residual line



Example 2:
Determine Ka



هون بطلع
ميل الـ residual هو
Ka

Ka =-slope*2.303 =0.3814*2.303

Ka= 0.878 hr⁻¹

* نلاحظ انه يختلف اختلاف بسيط بين الـ Residual و الـ terminal.

Example 2

* ممكن انقسم ($\frac{Vd}{F}$)

- Volume of distribution (normalized for bioavailability):
- From the terminal line best fit line, [intercept] = 1.359.

K = 0.2
Ka = 0.878

(لانه log) $10^{Intercept} = \frac{Ka \cdot F \cdot D}{Vd(Ka-K)}$

$$\Rightarrow \frac{Vd}{F} = \frac{Ka \cdot D}{10^{Intercept}(Ka-K)} = \frac{0.878*500}{10^{1.359}(0.878-0.2)} = 28.3\ L$$

من تسجيل المودل دقيقة ٣٦, لشرح هاد السؤال

Example 3

Vd = 40 L
X_0 = 500 mg
F = 0.8
K = 0.2 hr^{-1}
Ka = 1.3 hr^{-1}

- A patient received a single dose of 500 mg erythromycin in the form of a tablet that is known to have 80% bioavailability. Calculate the time to reach the maximum concentration (1.7 hr), the maximum conc (7.11 mg/L), AUC (50) and Clearance (8 L/hr) after this single dose If K is 0.2 hr^{-1}, Ka is 1.3 hr^{-1}, and Vd is 40 liters.

[الجواب موجود بالحل النهائي]

Examples:

100 mg

Q1: (=Q7 in Applied BP & PK)
A single oral dose, 100 mg, of an antibiotic was given to an adult male patient (43 years, 72 kg). From the literature, the pharmacokinetics of this drug fit a one-compartment open model. The equation that best fits the pharmacokinetics of the drug is:

* من الـ equation بطلع الـ K و Ka

$$Cp = 45(e^{-0.17\times t} - e^{-1.5\times t})$$

(K = 0.17, Ka = 1.5)

From the equation above, calculate **(a)** t_{max} **(b)** Cp_{max} , and **(c)** $t_{1/2}$ for the drug in this patient
Assume Cp is in µg/mL and the first-order rate constants are in $hours^{-1}$.

① $t_{max} = \frac{\ln(\frac{Ka}{K})}{Ka - K} = \frac{\ln(\frac{1.5}{0.17})}{1.5 - 0.17} =$

② بس أعوض بالمعادلة $C_{max} = 45(e^{-0.17x} - e^{-1.5x}) =$

③ $t_{1/2} = \frac{0.693}{K} = \frac{0.693}{0.17} =$

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Q2: (=Q8 in Applied BP & PK)

Two drugs, A and B, have the following PK parameters after a single oral dose of 500 mg:

Drug	k_a (hr^{-1})	k (hr^{-1})	V_D (mL)
A	1.0	0.2	10,000
B	0.2	1.0	20,000

* هون الـ F ما بندخلها زي لما ماكنا بندخلها بالـ IV bolus

Both drugs follow a one-compartment PK model and are 100% bioavailable = 1

a. Calculate the t_{max} for each drug.

b. Calculate the Cp_{max} for each drug.

a. $t_{max(A)} = \frac{\ln(\frac{ka}{k})}{ka-k} = \frac{\ln(\frac{1}{0.2})}{1-0.2} = 2.01$

$t_{max(B)} = \frac{\ln(\frac{0.2}{1})}{0.2-1} = 2.01$

b. $C_{max(A)} = \frac{Ka \times F \times X_0}{Vd(Ka-K)} \times [e^{-K t_{max}} - e^{-Ka\, t_{max}}]$

$\frac{1 \times 1 \times 500}{10(0.8)} * [e^{-0.2 \times 2.01} - e^{-1 \times 2.01}] =$

$C_{p(max)(B)} = \frac{0.2 \times 1 \times 500}{20(-0.8)} \times [e^{-1 \times 2.01} - e^{-0.2 \times 1}] =$

Q4: (5V) *

Drug X is used for the treatment of ventricular tachyarrhythmia. It is administered intravenously, orally and intramuscularly, and its therapeutic range is 4 to 8 µg mL^{-1}. When a 750 mg dose is administered intravenously to a *normal healthy subject*:

- The elimination half life = 3 h
- The apparent volume of distribution = 140 L

* فكرة هاد السؤال انو اعطاني الـ elimination half life (t½) و (Vd) للـ (IV) وبقدر استعملهم للـ oral

بكبنا هاي الـ Parameters ما بتتغير باختلاف الـ route of administration حتى بقدر اطبقها ع كوانين الـ IV bolus والـ Oral.

Q4-Cont'd:

When a tablet containing 250 mg of drug X is administered orally to a normal healthy subject:

- The absorption rate constant (Ka) = 2.8 h^{-1}
- The intercept of the plasma concentration time profile (on S.L. graph)= 1.665 µg/mL
- The fraction of dose absorbed (i.e. reaching the general circulation)= 85.54%

$\frac{Ka\,F\,X_0}{Vd(Ka-K)}$

لو اعطتني الـ log بحط $10^{intercept}$

0.8554

Note ← * بتزكر بالسؤال ، حش هناك بالسلايد اللي قبل هاي حكالي انه normal healthy وبرضو هون بس أعطى الدواء اعطى لـ normal heathy [يعني نفس المريض]

هاد يعني الـ K / $t_{0.5}$(elim) / Vd مش رح تختلف وحققت شرط :-

are constant for a particular drug adminstrated to a particular patient

← * بس لو أعطاني مريضين (مريض (1) و مريض (2)) ما بقدر أطبق نفس (Vd / $t_{0.5}$(elim) / K)

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Determine the following from the available information:

1. t_{max} and Cp_{max} following the administration of a 250 mg and 500 mg tablet
2. Whether the administered oral dose (i.e. 250 mg tablet) will provide the peak plasma concentration high enough to control arrhythmia.
3. If not, how many tablets (250 mg strength) will be required to control arrhythmia?

إذا اعطيتو الـ 250mg رح اوصل للـ Cmax ولا ؟؟

يعني اذا طلع بالفرع الثاني انه الـ 250mg مش كافيه لـ أوصل لـ Cmax كم tablet. بحتاج من 250mg عشان أعمل control على arrhythmia.

X 4. Determine the absorbable amount of drug remaining at the site of administration and the amount of drug in the body and/or blood at a time when the rate of absorption is equal to the rate of elimination for extravascularly administered dose of 500 mg via tablet.

X 5. Determine the rate of absorption and the rate of elimination, at peak time, following the administration of a 250 mg and a 500 mg tablet

① $t_{max} = \frac{\ln(Ka/K)}{Ka - K} = \frac{\ln(\frac{1.3}{0.2})}{1.3 - 0.2} =$

② $C_{max} = \frac{ka \cdot x F x D_0}{Vd\,(ka - K)} \times [e^{-K t_{max}} - e^{-ka\, t_{max}}]$

$= \frac{1.3 \times 0.8 \times 500}{40 \times 1.1} \times e^{-0.2X} - e^{-1.3X}$

③ $AUC = \frac{F x D_0}{K x Vd} = \frac{0.8 \times 500}{0.2 \times 40}$

④ $CL = K x Vd = 0.2 \times 40 = 8$

1000 ng).
25 mg tablet, $(C_p)_{max} = 6.476$ ng mL^{-1} (6.476 µg L) (calculated method)
50 mg tablet, $(C_p)_{max} = 11.63$ ng mL^{-1} (calculated method).
Once again, note the approximate directly proportional relationship between the peak plasma concentration and the administered dose.
The intercept values for the plasma concentration versus time profiles are as follows:

Answers to problem-solving exercises

1 a. $t_{max} = \frac{\ln(K_a/K)}{K_a - K} = \frac{\ln(2.8\ h^{-1}/0.231\ h^{-1})}{2.8\ h^{-1} - 0.231\ h^{-1}}$

$t_{max} = \frac{2.4949}{2.569\ h^{-1}}$

$t_{max} = 0.971$ h or 58.25 min for a 250 mg dose.

Note that since peak time is *independent of the dose administered*, for a 500 mg tablet, the peak time will be identical (i.e., 0.971 h or 58.25 min). However, if an identical dose or even a different dose of procainamide is

حل السؤال الرابع من الكتاب

administered through a different extravascular route (e.g., intramuscular), different dosage form (e.g., solution, capsule, controlled-release tablet) or different formulation (e.g., tablet made by a different manufacturer or the same manufacturer with a different formulation), the peak time may be different. This is because the absorption rate constant may change with route of administration, dosage form, and formulation.

b. $(C_p)_{max}$ is given by

$$(C_p)_{max} = I(e^{-Kt_{max}} - e^{-K_a t_{max}})$$

where I is the y-axis intercept of the line extrapolated from the terminal linear segment of the plasma concentration versus time curve on semilogarithmic coordinates. We know from the available information that the absorption rate constant (K_a) and the elimination rate constant (K) are 2.8 h^{-1} and 0.231 h^{-1}, respectively, and the calculated peak time is 0.971 h. The intercept of the plasma concentration versus time data for a 250 mg tablet is reported to be 1.665 µg mL^{-1}. Substituting these values in the equation will provide $(C_p)_{max}$:

$$\begin{aligned}(C_p)_{max} &= 1.665\ \mu g\ mL^{-1} \times (e^{-0.231\times0.971} - e^{-2.8\times0.971}) \\ &= 1.665\ \mu g\ mL^{-1} \times (e^{-0.2243} - e^{-2.7188}) \\ &= 1.665\ \mu g\ mL^{-1} \times (0.7990 - 0.06595)\end{aligned}$$

$(C_p)_{max} = 1.220$ µg mL^{-1} for a 250 mg dose.

2 The therapeutic range for the drug is 4–8 µg mL^{-1}. This, therefore, suggests that 250 mg dose is insufficient to produce the pharmacological effect and a larger dose will be needed. Furthermore, the relationship between the peak plasma concentration and the dose administered is directly proportional (linear

3 Administration of four to six tablets of 250 mg strength or three tablets of 500 mg strength or two tablets of 750 mg strength, however, will yield procainamide plasma concentration of 4.88 µg mL^{-1} for the 1000 mg dose and 7.32 µg mL^{-1} for a 1500 mg dose (linear pharmacokinetics) (within the therapeutic range).

4 When the rate of absorption (K_aX_a) is equal to the rate of elimination (KX), $t = t_{max}$; in other words, rate of absorption and rate of elimination become equal *only at peak time*:

$$(X_a)_t = FX_0e^{-K_at}.$$

The absorbable fraction F is 0.8554, or 85.54%.
When $t = 0$; $e^{-K_at} = 1.0$; and $K_a = 2.8$ h^{-1}.
Therefore, for a 250 mg dose, the absorbable amount of drug at the site of administration at $t = 0$ is $(X_a)_{t=0} = 0.8554 \times 250$ mg $\times\ 1 = 213.85$ mg.
When $t = t_{max}$,

$$F(X_a)_0 = 213.85\ mg.$$

At t_{max},

$$(X_a) = F(X_a)_0e^{-K_at_{max}}$$

where t_{max} 0.970 h and $K_a = 2.8$ h^{-1}.
So at t_{max}

$$\begin{aligned}(X_a) &= 213.85\ mg \times e^{-2.8\times0.970} \\ &= 213.85\ mg \times e^{-2.716} \\ &= 213.85\ mg \times 0.066138.\end{aligned}$$

At t_{max}, $(X_a) = 14.14$ mg (the absorbable amount of drug remaining at the site of administration at peak time).
Therefore, for the 500 mg dose (linear pharmacokinetics), the absorbable amount of drug remaining at the site of administration at peak time is 24.28 mg.
The amount of drug in the blood $(X)_{max}$ at peak time: