Rate of reaction

محاضرة (2)

Rate of reaction :-

→ [Rate of reaction :- (سرعة التفاعل)

$$\frac{\text{التغير في كمية معينة}}{\text{التغير في الزمن}}$$

* لو عندي المادة A تحولت الى B ف Rate هو سرعة تحول المادة من A ← B

$$A \longrightarrow B$$

في السرعة :- $\frac{\ominus \Delta A}{\Delta t} = \frac{\oplus \Delta B}{\Delta t}$ (A تقل ← ⊖) (بتزيد → ⊕)

ليه هيك :- لإنه فش مباشرة تحولت A الى B

تحولت بشكل تدريجي

ف مع الوقت الـ A رح تقل والـ B

رح تزيد هاد كلي بصير بالكانتك

بس ما بنحتلوا (A و B).

بالكانتك رح كلي amount ← $A_0 \longrightarrow A_t$

↓↓ هاي الـ Parent drug

↑↑ هاي الـ metabolite.

إحنا حكينا اي دواء كلوي ع excipent. + active ingredients

هاد اللي بهمني

A	B	t
100	0	0
50	50	2

$\frac{dA}{dt} = \frac{100-50}{0-2} = \ominus 25$

تدل على انه A بتقل

$\frac{dB}{dt} = \frac{0-50}{0-2} = \oplus 25$

تدل على انه B بتزيد

وهاد هيك مفهوم (Rate)

* افهموا الـ Rate حتى تقدروا بتمفهوا الـ (zero order / First order.)

- حكينا انو احنا ممكن نتعامل مع (amount) و (concentration)

اذا حكيت عندي مادة معينة دخلت من الـ oral راحت للـ Stomch وصلت لـ small intesting مرت (A)

absorption → systemic circulation

$A_1 \rightarrow A_2$

بالدم — بالامعاء

Pharmakokinetik بالـ Rate of reaction للادوية هناتو بس أدرس

لهي التغير بكمية الدواء ضمن وقت معين أو التغير بالتركيز

$\frac{d[A]}{d[t]}$

Example: طب هاد لمثال بحكي عن تغير مادة A من time zero ع بعد اعتبرنا

(1) * كيف حسبنا Rate ؟

A_1	B_2	t
100	50	0
200	150	
400	350	

لو ضاعفنا الجرعة

بنحسب بس ضاعفنا.

$\frac{dA}{dt} = \frac{100-50}{0-2} = \boxed{-25}$

$\frac{200-150}{0-2} = \boxed{-25}$

$\frac{400-350}{0-2} = \boxed{-25}$

طب شو معنى هاد كلي ؟ ☺

اللحية اللي حسبتها هي Rate وهيك التغير بناء المادة هو نفسه

[هيني بتناقص بمقدار 25 ⊖ بتناقص].

[الوحدة ثابتة] ← حتا لو ضاعفت الجرعة الأولية.

* هيني زي ما حكينا قبل شوية كول من (A→B) حوض النظر عن الـ A اللي أنا أعطيتها.

Rate ← [Constant] [-25] حوض النظر عن الجرعة الأولية

هاد الـ Rate اللي عنا بالـ [Pharmakokinetiks] بنحكي عنه

[Rate of elimination]

هاد إلـ Rate كونو ثابت بنسمي

[Zero oroler Kinetics]

في الـ (zero order) :-

الـ Rate ما بعتمد ع التركيز الأولي، لانه بعض عن التركيز اللي بعطي للجزء

الـ Rate بضل ثابت

* بالمحفوظ الـ Rate بتناسب طردي مع Concentration اللي بعطي

بس بالـ zero order ما بعتمد ع التركيز الأولي

Rate $\propto [A]^0 = 1$

$\frac{-dA}{dt}$ → * ما حطيت اللي تم انتاجه, حطيت (metabolite)

* الـ active ingredients هي بتهمني

$\frac{dA}{dt} = -K$

[Zero order kinetic reaction]

Example(2)

$t=0$ A_0	A_2 $t=2$
100	50
200	100
400	200

هناخفت الجرعة

↓ التركيز تابع للدواء بالجسم

$$\frac{dA}{dt} = \frac{A_0 - A_2}{t_0 - t_2}$$

end Point (1) :- $\frac{100-50}{0-2} = 25$

end Point (2) :- $\frac{200-100}{0-2} = 50$

end Point (3) :- $\frac{400-200}{0-2} = 100$

الوحدة لـ Rate :- mg/h

لهلا أنا هون قاعد بحكي عن amount مش conc

← بنلاحظ بهاد المثال إنه (Rate) متغير (مش ثابت وكمان بزيد مع الوقت) ← بالمثال الأول كان ثابت

نستنتج انه Rate اذا حكي عن ← [first order]

↓

كون مش Constant rate of elimination.

$$Rate \propto [A]^1$$

$$Rate = K[A]$$

$$\frac{dA}{dt} = -K[A] \longrightarrow$$ [first order Kinetic reaction]

Scanned with CamScanner

Zero order	First Order
$\frac{dA}{dt} = -K$	$\frac{dA}{dt} = -K\,[A]$
Rate of elimination (Constant)	Rate of elimination (not constant)

[First order / Zeuroorder] equation ل علوا تكامل وتفاضل ← * الطريقه بالزبط موجود بالكتاب اذا بدهم اياها ☺

مطلع بالمواد → $A_t = A_0 - K_0\, t$ → zero order

amount لو بدي conc ← $C_t = C_0 - k_0\, t$

$\ln [A_t] = \ln [A_0] - Kt$ → First order

$\ln [C_t] = \ln [C_0] - kt$

نفس ال ln اكى log زي ما عطانا قبل →

$$\frac{\log A_t \times 2.303}{2.303} = \frac{\log A_0 \times 2.303}{2.303} - \frac{kt}{2.303}$$

$$\log [A_t] = \log [A_0] - \frac{kt}{2.303}$$

e مع ln بتروح ← $e^{(\ln[A_t])} = e^{(\ln[A_0] - kt)}$ لو أخذنا الـ e للطرفين

$[A_t] = [A_0] - e^{-kt}$ → first order

في الـ first order

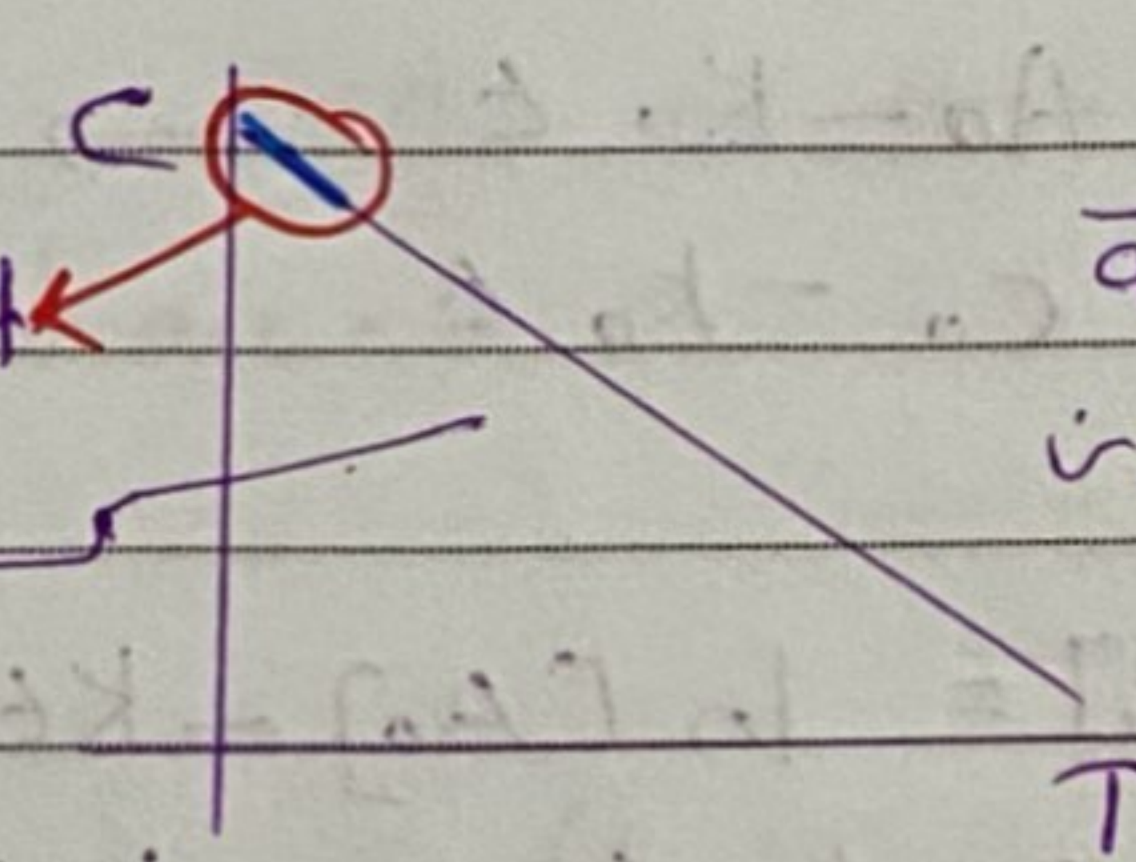
$\ln[A_t] = \ln[A_0] - kt$

$\log[A_t] = \log[A_0] - \frac{kt}{2.303}$

$[A_t] = [A_0] - e^{-kt}$

لو رجعنا للـ Zero order

$C_t = C_0 - kt$



هاد الخط نفسه slop نفسه الـ Rate.

هيك رسمة الـ Zero order بكون linear لأنه الـ rate of elimination بكون (constant)

أعطانا الـ -k negative

$y = m x + b$ → C_0 (معناه التركيز لما t = zero كون C.) → معادلة الخط المستقيم

m ↓ (الميل) slop ; x ↓ time ; b ↓ intercept

$= \frac{C_0 - C_2}{0 - 2}$ → نفس الميل

(بيضل أخذ اي نقطتين ع Line)

طب لو رجعنا ع (first order) [اي ماخذ ln او log]

لانه هادا رسم اي رسمنا رسم

بياني عادي، ورقة رسم

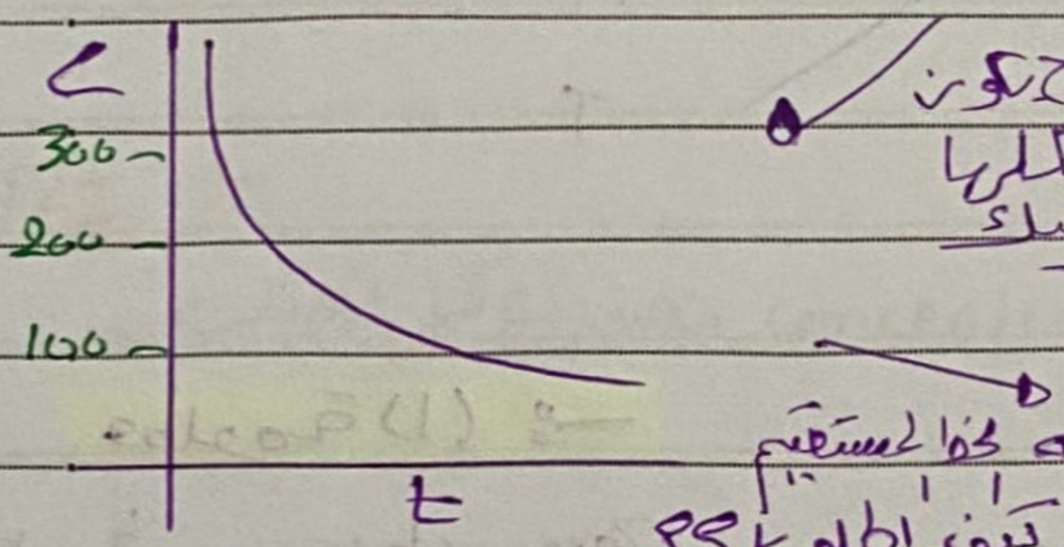
اي رسم عليها.

logarithm expression

linear او expression

هي مختلفة عن ورقة الرسم العادي

فرح نولد هاي $[A_t] = [A_0] - e^{-kt}$



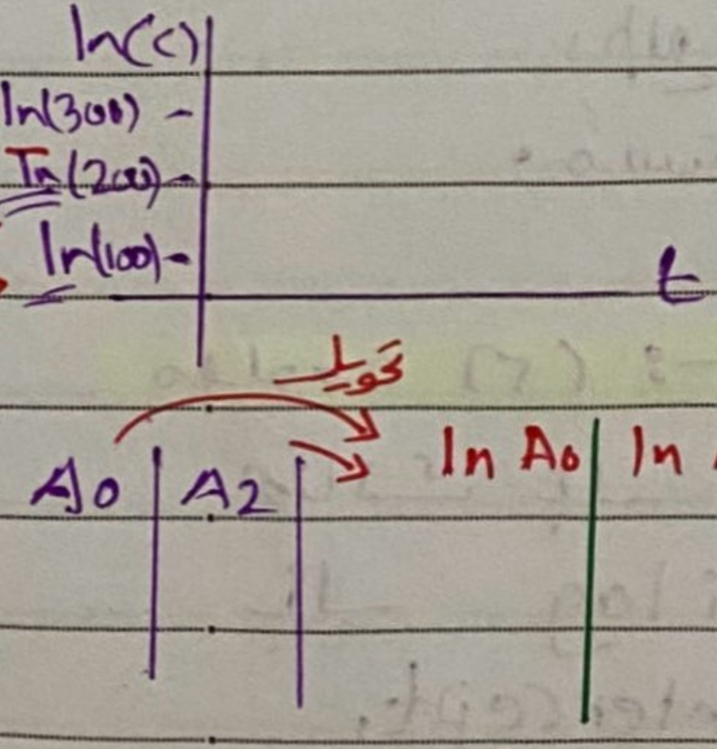
رح تكون شكلها هيك

* هون ما بقدر امشي ع معادلة الخط المستقيم

طب كيف بدي أطلع الـ slop كيف اطلع k؟؟

[عن طريق log او ln].

عن طريق ln

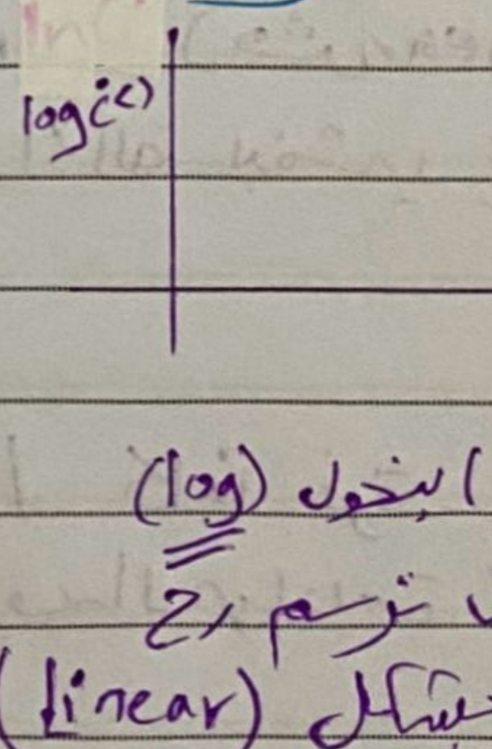


$$slop = \frac{\ln(C_0) - \ln(C_2)}{t_0 - t_2}$$

ع فرض القيم اللي هون حولناهم

بتطلع معي لرسمة بشكل linear

عن طريق log



نفس مبدأ (ln) بنحول (log)

وبرضو هون رح نرسم رح

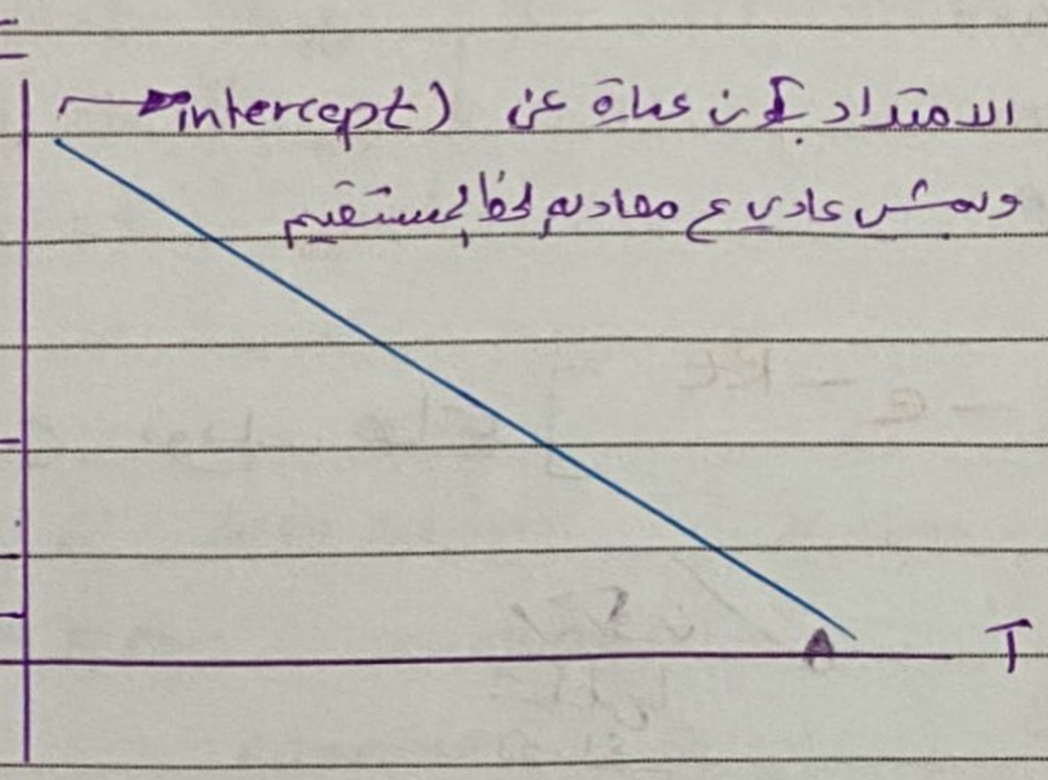
بطلع معي شكل (linear)

$$slop = \frac{\log(C_0) - \log(C_2)}{t_0 - t_2}$$

طب لطريقة اللي كنا بنفكر فيها فيل شوي بتحسوا ح
= ضيع وقتكم صح ☺ ؟

تعالوا نشوف طريقة تانية واسمها (Semi-log) $\frac{25-0}{25-0}$

القيم لوجود ع (y) انا مش محتاج اروح ابدرهم واخد الـ log تاعهم.



نلاحظ انو الارقام بالـ semi-log بتاعتها بيبقوا مش متساوية لأنه اصلا هو محوله لـ Log

معلومة (1) :-

* في Zero order بطلع بس ارسم ع Rectangular graph ← Linear

* في first order بطلع بس ارسم ع Rectangular graph ← curve (linear مش) ومستحيل بأي الحالة بنمشي ع معادلة الخط المستقيم

معلومة (2) :-

هناك بال ln و log كانا فرق الصفات و log و ln بال semi log الفرق بالصفات كان بـ (C) اللي هو intercept.

معلومة (3) :-

1% تتكون الأدوية ← Zero order,

99% تتكون الأدوية ← First order.

مهم جداً أعرف الـ Slop :-

$C_t = C_0 - K_0 t$ Slop = $-K_0$

$\ln[C_t] = \ln[C_0] - kt$ Slop = $-K$ ← الحل فقط لمعادلة خط مستقيم لأنه بصار رسمته ع Rectangular طلع معي linear

$\log[A_t] = \log[A_0] - \frac{kt}{2.303}$ Slop = $\frac{-k}{2.303}$

$t_{1/2}$:-

↳ يكون عندها concentration نصف التركيز الأصلي ،

زميلتكم ريماس الشوابكة .

وَأَن لَّيْسَ لِلْإِنسَانِ إِلَّا مَا سَعَىٰ

PK models and basic PK calculations

PK theory material lecture.2

بس ادرسوهم ☺

* الكلمات المظللة بالسلايدات مهمين، هم عبارة عن الـ keyelements للامتحان.

* في أول كم سلايد حكتها الدكتورة أمجاد ما مهمين (رح أحكي من وين المهم ع سلايدات).

* (First order / Zero order) ← مهمين كثير وحيجي عليهم اسئلة كثيرة بالامتحان

[طيب أول اشي ادرسوا من الدفتر وارجعوا لـ السلايدات هتلاقوا كل شي مفهوم بالسلايدات ان شاء الله ☺]

Importance of PK

أول اشي ع مستوى الحيوان بعدين الإنسان

* Knowledge of the pharmacokinetic behavior of drugs in animals and human is crucial in drug development, both to make sense of preclinical toxicological (side effect) and pharmacological data and to decide on an appropriate dose and dosing regimen for clinical trials.

* Drug regulators have developed concepts such as bioavailability and bioequivalence to support the licensing of generic versions of drugs produced when originator products lose patent protection.

بدي أشوف الـ effect.

براءة الاختراع

(نقارن الدواء القديم مع الدواء الجديد)

اتفقنا انه bioavailability تفرق عن absorption.

absorption ↓ حركة هذا الدواء من المكان الي اعطيته فيه الدواء ← systemic circulation

كم الجسم أخذ من هاي الجرعة.

← الها نوعين

absolute: بدي اقارن الدواء مع IV route

relative: بدي اقارن الدواء مع أي route.

Importance of PK

• Understanding the general principles of pharmacokinetics is also important in clinical practice, to understand the **rationale of recommended dosing regimens**, to interpret drug concentrations for TDM and to adjust dose regimens rationally, and to identify and evaluate possible drug interaction.

• In particular, intensive-care specialists and anesthetists dealing with a severely ill patient often need to individualize the dose regimen depending on the urgency of achieving a therapeutic plasma concentration, and whether the pharmacokinetic behavior of the drug is likely to be affected by illness such as renal impairment or liver disease.

Basic Pharmacokinetics and Pharmacokinetic model

• Drugs are in a dynamic state within the body as they move between tissues and fluids, bind with plasma or cellular components, or are metabolized. The biologic nature of drug distribution and disposition is complex, and drug events often happen simultaneously.

• Such factors must be considered when designing drug therapy regimens. The inherent and infinite complexity of these events requires the use of mathematical models and statistics to estimate drug dosing and to predict the time course of drug efficacy for a given dose.

PK models

- Model: a hypothesis using mathematical terms to describe quantitative relationships concisely.

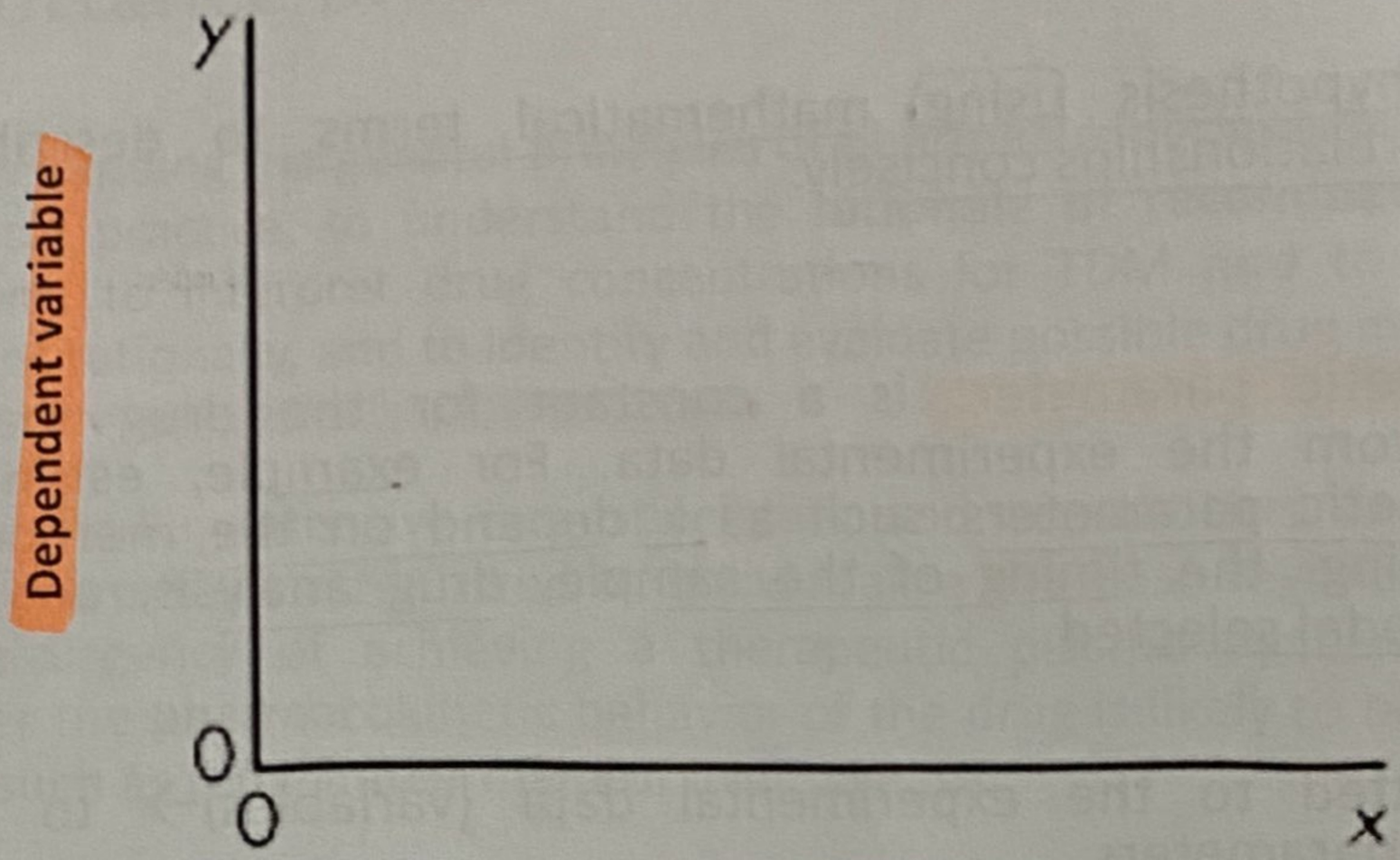
- Pharmacokinetic parameter: is a constant for the drug that is estimated from the experimental data. For example, estimated pharmacokinetic parameters such as k depend on the method of tissue sampling, the timing of the sample, drug analysis, and the predictive model selected.

- Model is fitted to the experimental data (variables)→ to estimate key parameters

Basic pharmacokinetics and pharmacokinetic model

- A pharmacokinetic function relates an independent variable to a dependent variable, often through the use of parameters.
- For example, a pharmacokinetic model may predict the drug concentration in the liver 1 hour after an oral administration of a 20-mg dose. The independent variable is the time and the dependent variable is the drug concentration in the liver. Based on a set of time-versus-drug concentration data, a model equation is derived to predict the liver drug concentration with respect to time.
- Such mathematical models can be used to describe and predict drug concentrations in the body as a function of time

Graphs



Compartmental PK

- Theoretically, an unlimited number of models may be constructed to describe the kinetic processes of drug absorption, distribution, and elimination in the body, depending on the degree of detailed information considered.

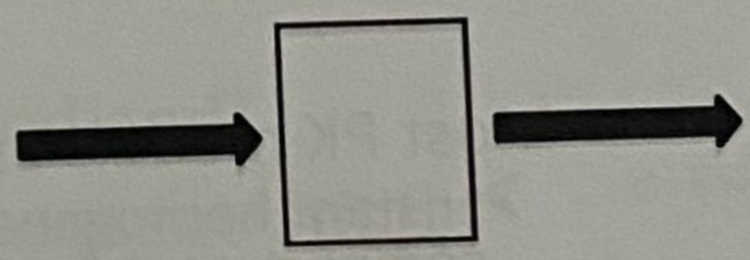
- A very simple and useful tool in pharmacokinetics is **compartmentally based models**.

- It is common and useful practice to divide objects of scientific interest into smaller conceptual units until the underlying mechanisms become apparent.

PK models

- Compartmental models are used, and they are simplified models in which the body is conceived to be composed of mathematically interconnected compartments (depicted as boxes)
- **Compartmental model are two types:**
  A. Empirically-based conventional models
  B. Physiologically-based pharmacokinetic (PBPK) models

Compartmentally-based model



* Simple
* The [drug] in the compartment for a given dose is determined by :

1- The fluid volume (V) of the comp.

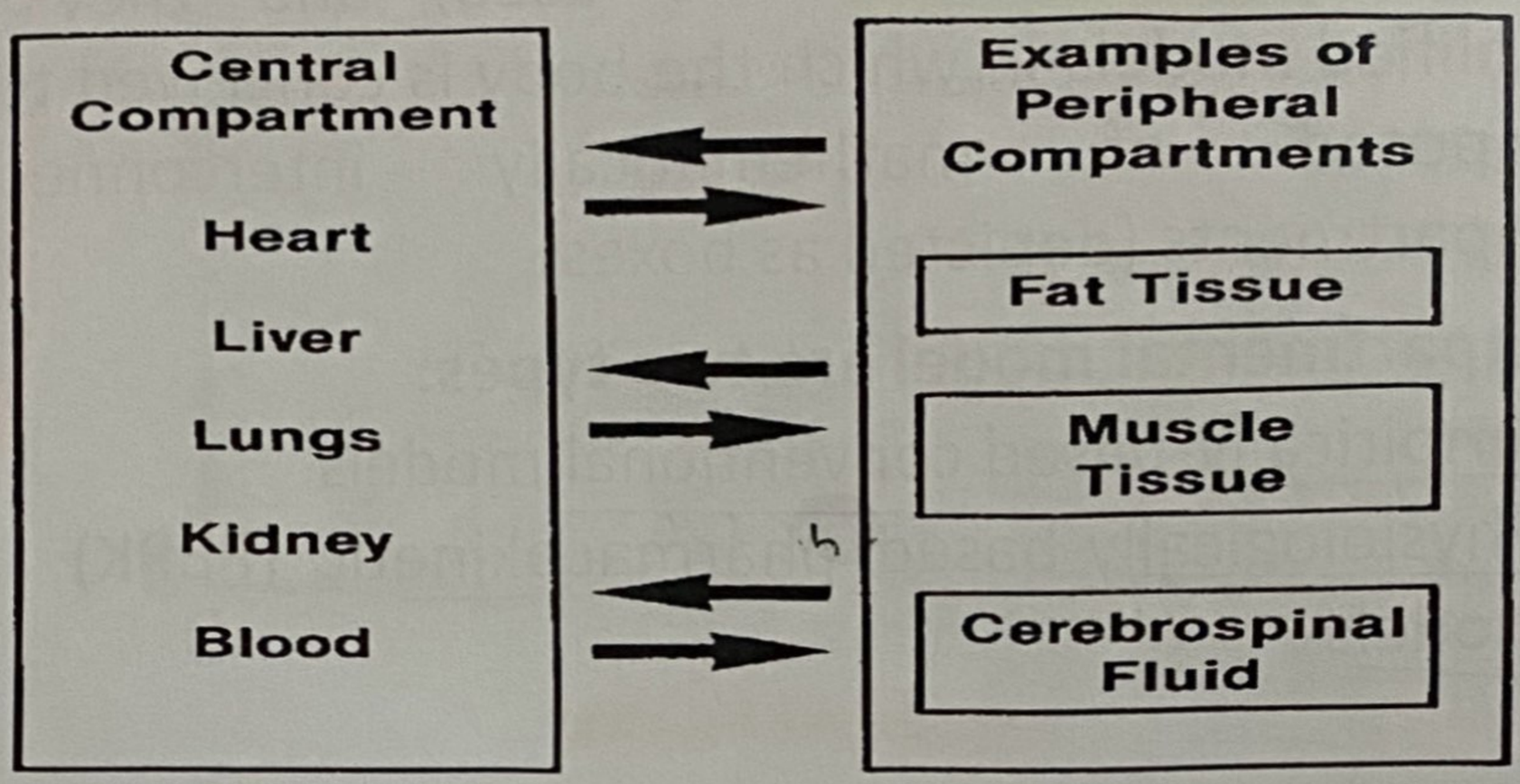
2- The elimination rate of drug per unit of time (k).

* One-compartment, two-compartment, or multi- compartment model.

* The compartments do not represent a specific tissue or fluid but may represent a group of similar tissues or fluids

Cont,

- Organs and tissues in which drug distribution is similar are grouped into one compartment.



Cont,

- Most PK models assume
  - instant homogeneous distribution of drug within each compartment "well-stirred"
  - and elimination rate constant does not change over time
- Model parameters (e.g. V and k) are determined experimentally from a set of drug concentrations collected over various times
- ⇧ parameters → ⇧complexity of the model
  - → ⇧ data needed
- Compartmental PK models are useful esp. when little information is known about the tissues

الوحدات/التحويل
جدول الاشيار
كثير مطمبين :)

1g = 1000 mg
mg = 1000 mg
1L = 1000 ml
1mL = 1000 m

Mathematical review

*amount هي نفسها → mass (g/mg/μg)

- Do you know?/ Can you?
- The units used usually for concentration?
- Calculate the amount of the drug in a solution with a known drug concentration and solution volume? In different volumes?
- **How to convert units?**
- e.g. mg/mL to g/L and μg/μL.
- Calculate the MW of the drug?
- Units of concentration in M?

M wt = g/mole
Molarity = moles/L
Molarity x M.W = Mole/L x g/mole
= g/L
هي نفسها ال Concentration.

* كل ما بتحل سؤال
حط المعطيات (مع الوحدات)
عشان ما تخربط بالتحويل

طريقة حساب ال concentration :-
① mass / V [هاي بدرح نحل عليها بالكاينتك].
② أو اضرب molarity x M.W

cont

- If a known amount of drug was added and resulted in 0.6 mg/L (for example) concentration of the solution, what volume of water was in the container?

0.6 mg/L

- For the following equation: (y=1.8x+2) (slop: 1.8, intercept: 2)

a.**Sketch** a plot of the equation.

b.If x = 0.5, what is y?

c.If y = 4.6, what is x?

cont

- What is the slope of the line that connects the following two points?
- 1) x=5, y=8.6
- 2) X=0.6, y=4.5

نوخذ فرض صادات عم فرق السينات

- Solve the following equations for *x*:
  - a. log x = 0.95
  - b. $e^x = 0.44$
  - c. ln x = 1.22

$10^{0.95}$

$e^x = 0.44 \times \ln^1$

$X = \ln(0.44)$

نوخذ ln

$\ln x = 1.22$

$X = e^{1.22}$

Basic exponent laws

- Expression: $N=b^x$

Laws of Exponents	Example
$a^x \cdot a^y = a^{x+y}$	$10^2 \cdot 10^3 = 10^5$
$(a^x)^y = a^{xy}$	$(10^2)^3 = 10^6$
$\frac{a^x}{a^y} = a^{x-y}$	$\frac{10^2}{10^4} = 10^{-2}$
$\frac{1}{a^x} = a^{-x}$	$\frac{1}{10^2} = 10^{-2}$
$\sqrt[y]{a} = a^{1/y}$	$\sqrt[3]{a} = a^{1/3}$

Logarithms

- If $N=b^x$, then $\log_b N = x$
- Common logarithms (log)= logarithms using base 10
- Natural logarithms (ln) use the base *e*

e ≈2.718

2.303 log N= ln N

- A logarithm does not have units = dimensionless

Laws of Logarithms

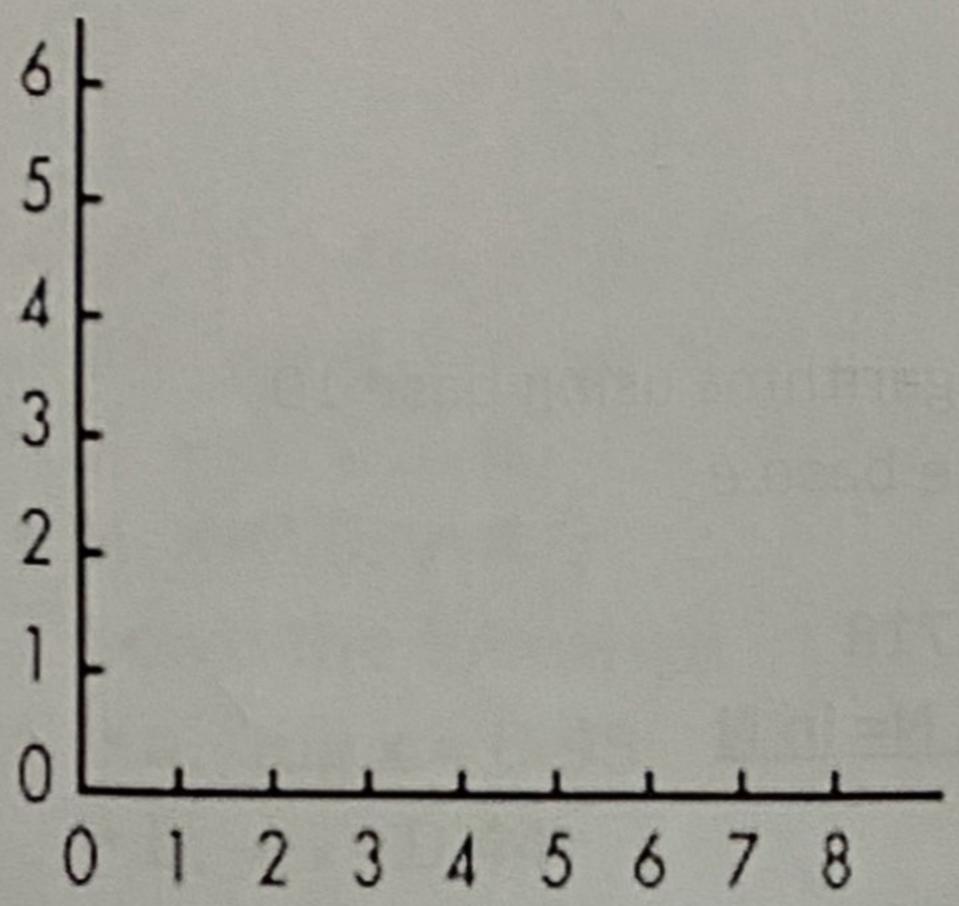
$$\log ab = \log a + \log b$$

$$\log \frac{a}{b} = \log a - \log b$$

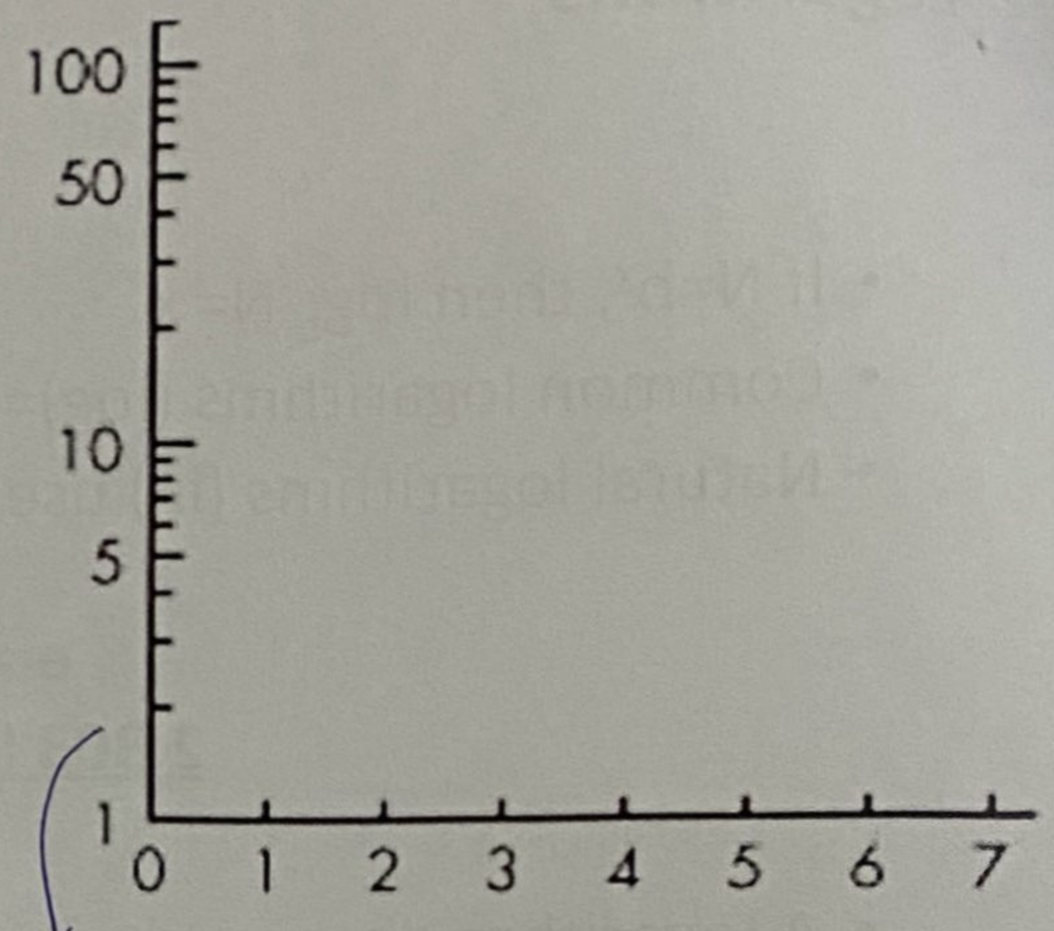
$$\log a^x = x \log a$$

$$-\log \frac{a}{b} = +\log \frac{b}{a}$$

- Your calculator → log, ln, anti-log and anti-ln



Rectangular coordinate graph



Semilog coordinate graph

نلاحظ بالـ Semilog المسافه بين الارقام مش متساويه لانه اصلاً احنا بنستخدم الـ (log)

cont

- Straight line eqt.

$$y = ax + b$$

- Slope? intercept?
- For a given straight line → calculate slope
  (on rectangular or semilog graph)
- **REMEMBER:**

In semilog graphs : the y values are plotted on a logarithmic scale **without** performing actual logarithmic conversions, whereas the corresponding x values are plotted on a linear scale

PK units

(مہمیت جدآ)

PARAMETER	SYMBOL	UNIT	EXAMPLE
Rate	$\frac{dD}{dt}$	$\frac{\text{Mass}}{\text{Time}}$	mg/hr
	$\frac{dc}{dt}$	$\frac{\text{Concentration}}{\text{Time}}$	µg/mL hr
Zero-order rate constant	k_0	$\frac{\text{Concentration}}{\text{Time}}$	µg/mL hr
		$\frac{\text{Mass}}{\text{Time}}$	mg/hr
First-order rate constant	k	$\frac{1}{\text{Time}}$	1/hr or hr^{-1}
Drug dose	D_0	Mass	mg
Concentration	C	$\frac{\text{Mass}}{\text{Volume}}$	µg/mL
Plasma drug concentration	C_p	$\frac{\text{Drug}}{\text{Volume}}$	µg/mL
Volume	V	Volume	mL or L
Area under the curve	AUC	Concentration x time	µg hr/mL
Fraction of drug absorbed	F	No units	0 to 1
Clearance	Cl	$\frac{\text{Volume}}{\text{Time}}$	mL/hr
Half-life	$t_{1/2}$	Time	hr

Rates and Orders of Reactions

- The rate of a chemical reaction of process is the velocity with which the reaction occurs. Consider the following chemical reaction:

Drug A ⇨ Drug B

- If the amount of drug A is decreasing with respect to time (that is, the reaction is going in a forward direction), then the rate of this reaction can be expressed as:

- dA/dt

- Since the amount of drug B is increasing with respect to time, the rate of the reaction can also be expressed as:

+ dB/dt

- The rate of a reaction is determined experimentally by measuring the disappearance of drug A at given time intervals.

Zero order reaction

- **Rate constants and order of Rx**
- Order of the Rx is the way that the [drug] affects the rate of the reaction or process
- Zero-order reactions or first-order reactions

$$- dA/dt = k*A^n$$

n → determine the rate of the reaction

*** Zero order reaction**

- Drug A is decreasing at a <u>constant</u> time interval t

n =0

$$dA/dt = - k_0*A^0$$
$$dA/dt = - k_0$$

k_0: is the zero-order rate constant

Unit of k_0 : **<u>mass/time</u>** (e.g. g/h)

$$dA/dt = - k_0$$

→Rearrange

→Integrate

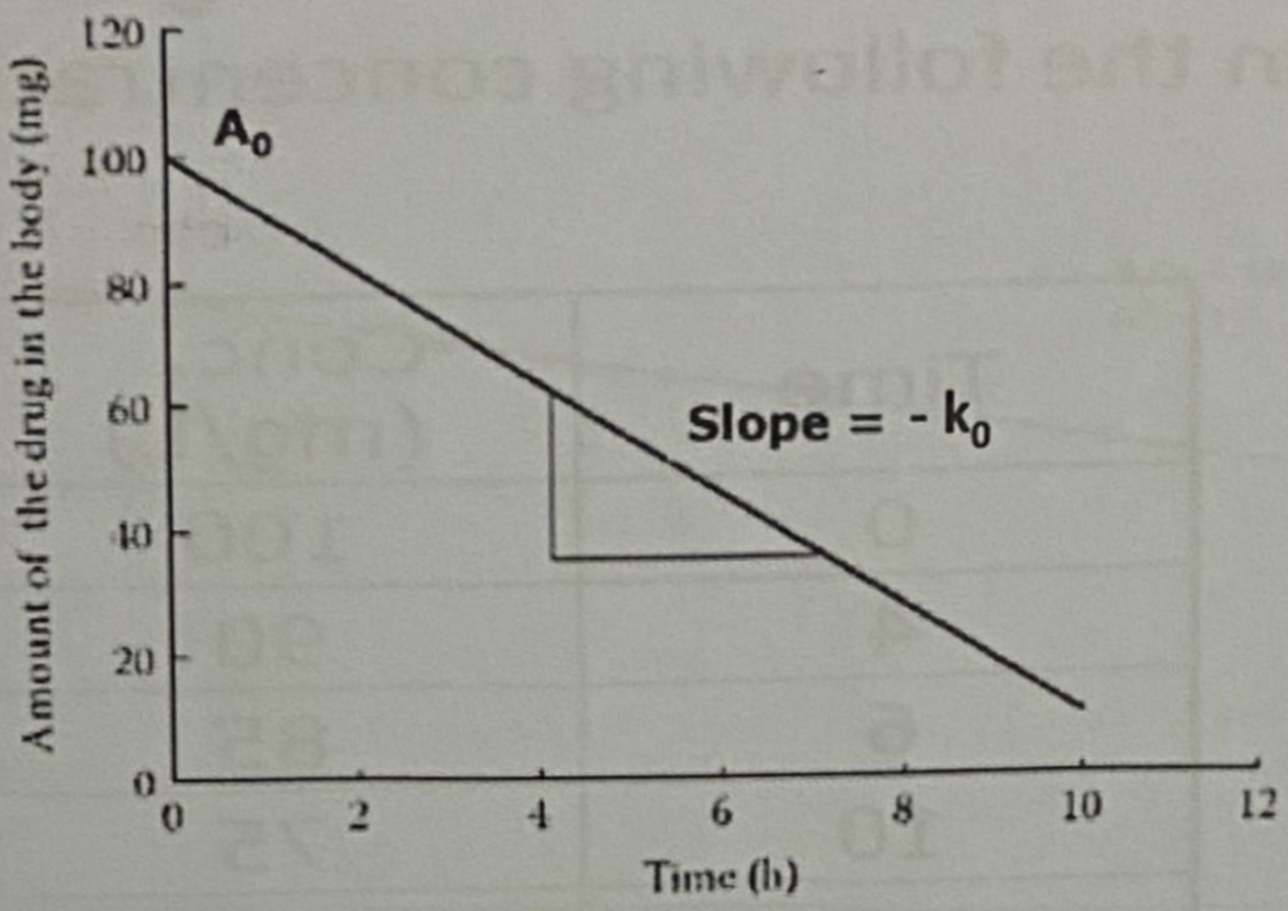
$$\boxed{A = - k_0 t + A_0}$$

A:

k_0:

A_0:

$$A = - k_0 t + A_0$$



Concentration → $C = - k_0 t + C_0$

Half-life($t_{1/2}$)- Zero order

- The period of time required for the amount (A) or concentration (C) of a drug to decrease by one- half.

- Zero-order half-life:

$$t_{1/2} = (0.5\ A_0) / k_0$$

- The zero-order $t_{1/2}$ is proportional to the initial amount or concentration of the drug (A_0) and is inversely proportional to the zero-order rate constant (k_0).

- **The time required for the amount to decrease by one-half <u>is NOT constant</u>**

Zero-Order Reactions: example

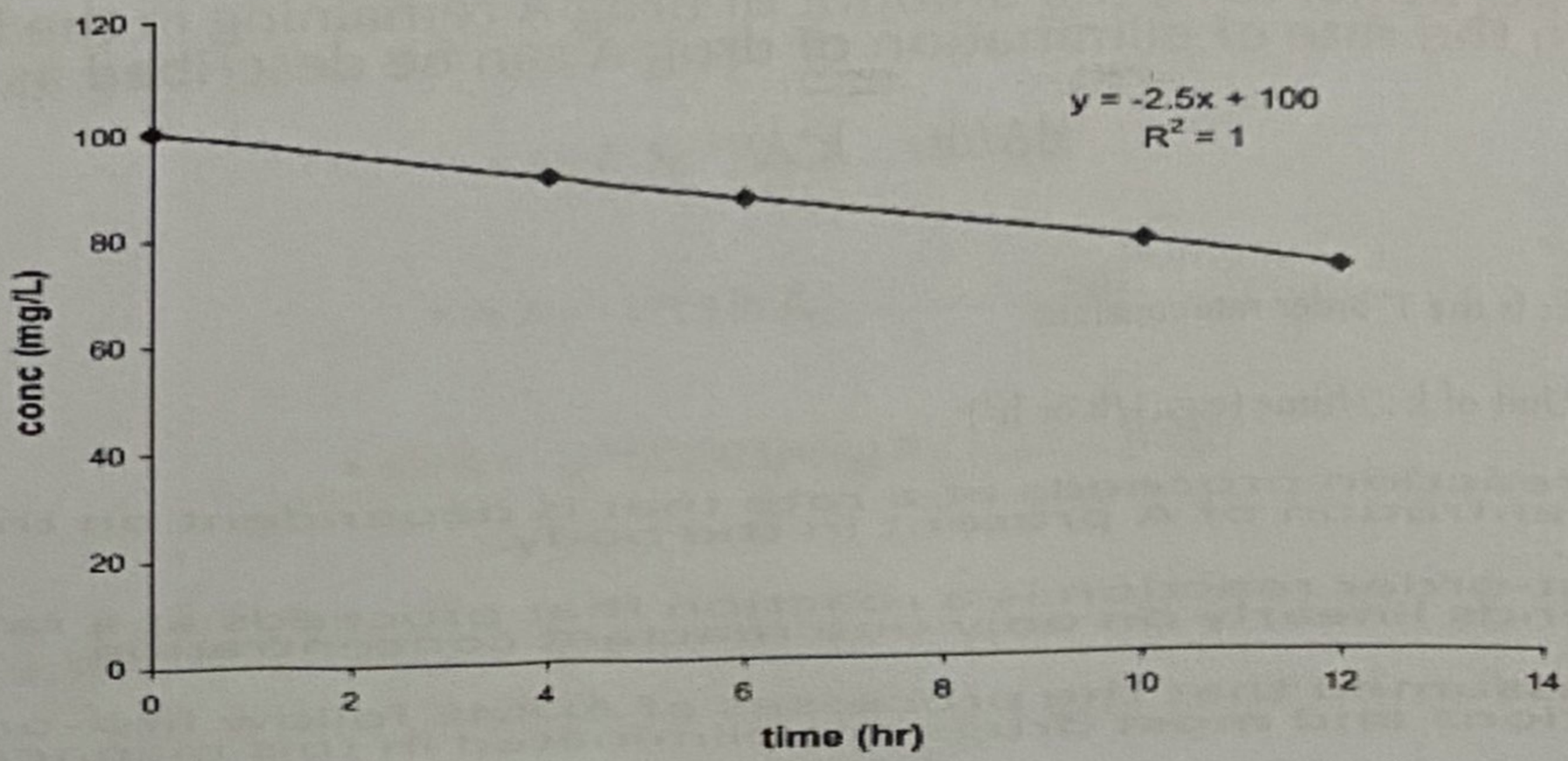
- **The administration of a 1000 mg of drug X resulted in the following concentrations:**

Time	Conc. (mg/L)
0	100
4	90
6	85
10	75
12	70

Zero-Order Reactions: example

- What is the order of the elimination process (zero or first)?
- What is the rate constant?

Zero-Order Reactions: example



Zero-Order Reactions: example

- Since the decline in drug conc. displayed a linear decline on normal scale, drug X has a zero order decline.

- From the equation displayed on the figure (intercept = 100, slope = -2.5)

- The elimination rate constant is 2.5 mg/hr

First order reaction

- If the amount of drug A is decreasing at a rate that is proportional to A, the amount of drug A remaining in the body, then the rate of elimination of drug A can be described as:

$$dA/dt = -k^{*}A^{1}$$

  - k: is the 1st order rate constant
  - Unit of k : 1/time (e.g. 1/h or h^{-1})

- The reaction proceeds at a rate that is dependent on the concentration of A present in the body.
- A first-order reaction is a reaction that proceeds at a rate that depends linearly on only one reactant concentration.
- It is assumed that the processes of ADME follow first-order reactions and **most drugs** are eliminated in this manner

First order reaction

- The amount of a drug with first order elimination is described according to the following equation:

$$A = A_0 e^{-k^{*} \cdot t}$$

where A is the amount of drug in the body, A_0 is the amount of the drug at time zero (equal to the dose in the case of IV bolus)

- This equation is equivalent to:

$$\ln(A) = \ln(A_0) - k^{*} \cdot t$$

- **$dA/dt = -k*A$**

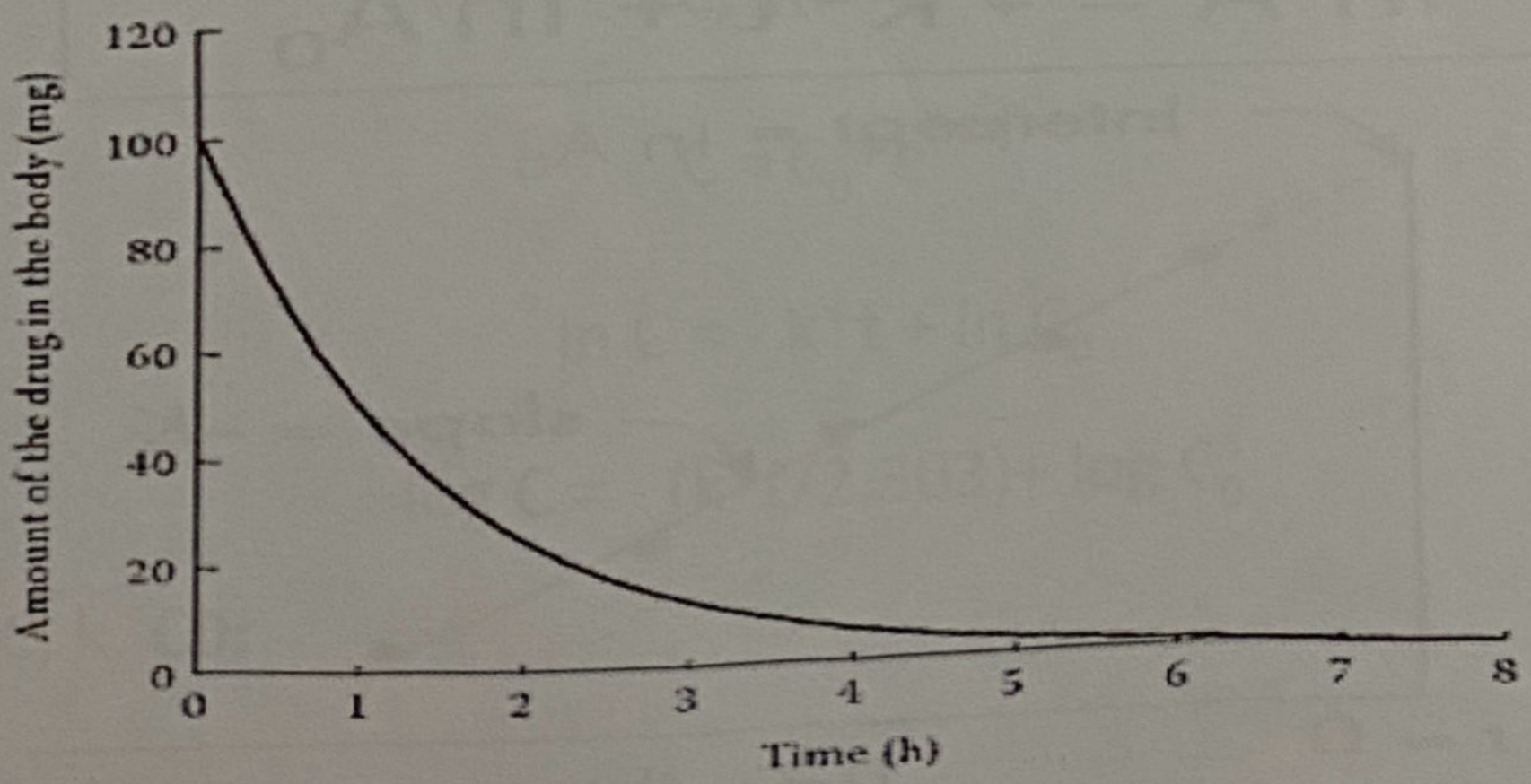
- $A = A_0 * e^{(-kt)}$.....[e]

- $\ln A = -k*t + \ln A_0$.....[ln]

- $\log A = -(k*t/2.303) + \log A_0$.....[log]

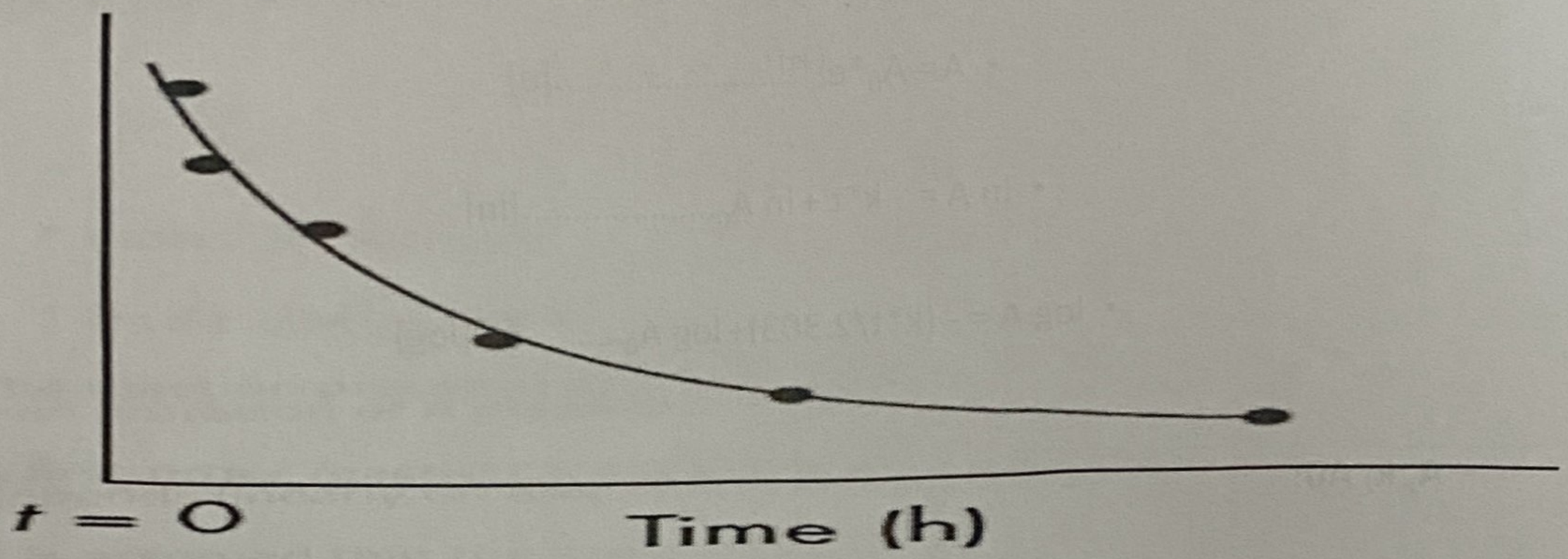
- **A, k, A0:**

Drug with first order kinetic



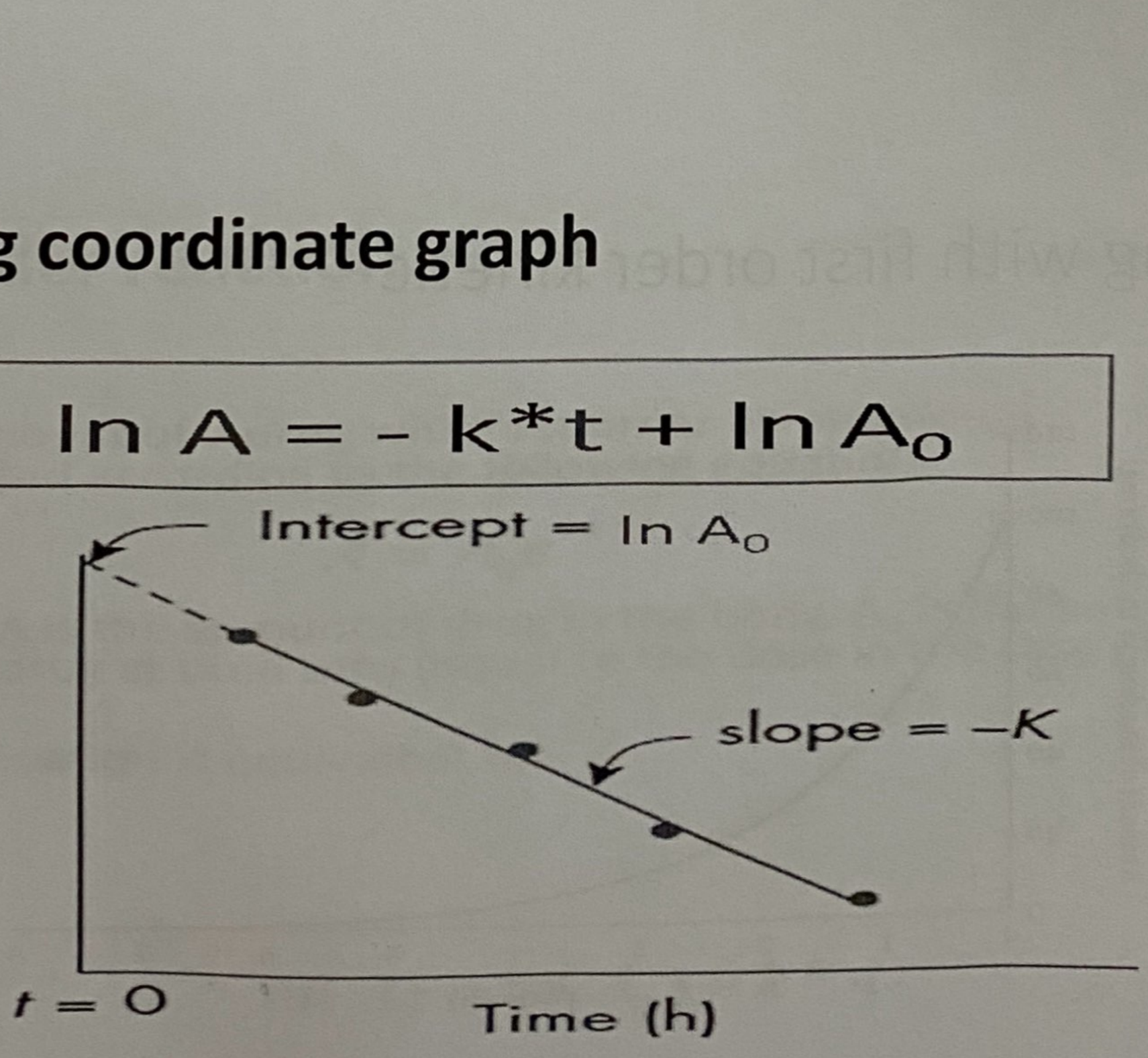
Rectangular coordinate graph

$$A = A_o * e^{(-kt)}$$



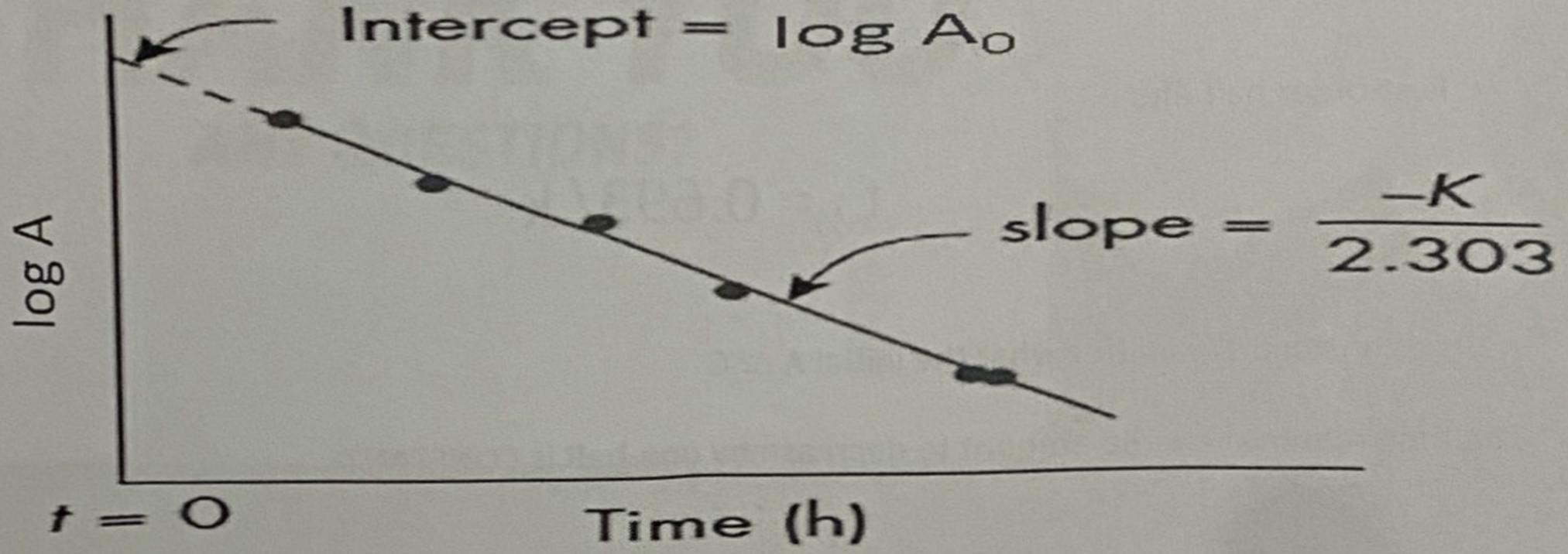
Semilog coordinate graph

$$\ln A = - k*t + \ln A_o$$



semilog coordinate graph

$$\log A = -(k*t/2.303) + \log A_0$$



cont

$$dC/dt = -k*C$$

$$C = C_0 * e^{(-kt)}$$

$$\ln C = -k*t + \ln C_0$$

$$\log C = -(k*t/2.303) + \log C_0$$

- **C, k, C0:**

cont

- The period of time required for the amount (A) or concentration (C) of a drug to decrease by one-half.

- First-order half-life:

$$t_{½} = 0.693 / k$$

- $t_{1/2}$ is a constant. No matter what the initial A or C
- **The time required for the amount to decrease by one-half <u>is CONSTANT</u>**