

PK models and basic PK calculations

PK theory material lecture.2

Importance of PK

* Knowledge of the pharmacokinetic behavior of drugs in animals and human is crucial in **drug development**, both to make sense of preclinical toxicological 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.

• فهم الأساس العلمي لأنظمة الجرعات الموصى بها.

• تفسير تراكيز الأدوية في الدم عند إجراء المراقبة العلاجية للدواء (TDM).

• تعديل أنظمة الجرعات بطريقة عقلانية ومدروسة.

• التعرف على التداخلات الدوائية المحتملة وتقييمها.

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 anesthesiologists 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.

على وجه الخصوص، يحتاج أطباء العناية المركزة وأطباء التخدير الذين يتعاملون مع مريض في حالة حرجة إلى تخصيص نظام الجرعات بشكل فردي، وذلك اعتمادًا على مدى الحاجة العاجلة للوصول إلى تركيز علاجي في بلازما الدم، وكذلك على ما إذا كان السلوك الحركي للدواء من المحتمل أن يتأثر بالحالة المرضية، مثل القصور الكلوي أو أمراض الكبد.

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.

إن التعقيد الجوهري وغير المحدود لهذه الأحداث يتطلب استخدام النماذج الرياضية والإحصاء لتقدير جرعات الدواء والتنبؤ بالمسار الزمني لفعالية الدواء عند إعطاء جرعة معينة.

- 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

النموذج (Model):

هو فرضية تُصاغ باستخدام مصطلحات رياضية لوصف العلاقات الكمية بشكل مختصر ودقيق.

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

المعامل الحركي الدوائي (Pharmacokinetic parameter):

هو ثابت خاص بالدواء يتم تقديره من البيانات التجريبية.

فعلى سبيل المثال، المعاملات الحركية الدوائية المقدرة مثل ثابت الإطراح (k) تعتمد على طريقة أخذ عينات الأنسجة، وتوقيت أخذ العينة، وطريقة تحليل الدواء، وكذلك على النموذج التنبؤي المختار.

- **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

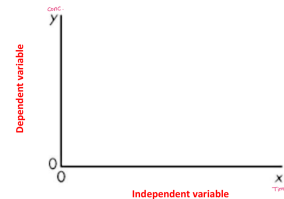
ملاءمة النموذج للبيانات:

يتم تطبيق (أو ملاءمة) النموذج على البيانات التجريبية (المتغيرات) بهدف تقدير المعاملات الأساسية المهمة.

Basic pharmacokinetics and pharmacokinetic model

$$\text{Amount (mass)} = \text{conc.} \cdot \text{when } V_d = 1$$

- 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



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

تُستخدم النماذج الحَجَرِيَّة (Compartmental models)، وهي نماذج مبسطة يُفترض فيها أن الجسم مكوَّن من حجيرات (مقصورات) مترابطة رياضيًّا، وغالبًا ما يتم تمثيلها على شكل مربعات في الرسوم التوضيحية.

- 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

أولًا: النماذج التقليدية المعتمدة على البيانات التجريبية (Empirically-based conventional models)
وهي نماذج تُبنى أساسًا على ملاءمة البيانات التجريبية دون الاعتماد بشكل مباشر على التمثيل الفسيولوجي الحقيقي لأعضاء الجسم.

ثانيًا: النماذج الحركية الدوائية المعتمدة على الأساس الفسيولوجي (Physiologically-Based Pharmacokinetic, PBPK models)
وهي نماذج تعتمد على تمثيل واقعي لأعضاء وأنسجة الجسم، حيث تُبنى على معلومات فسيولوجية فعلية مثل تدفق الدم، حجم الأعضاء، وخصائص الأنسجة، مما يجعلها أقرب للواقع البيولوجي.

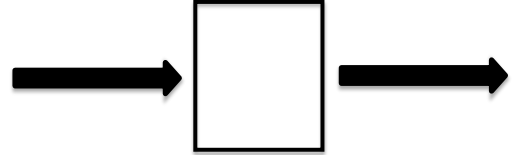
Compartmentally-based model

- * 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).

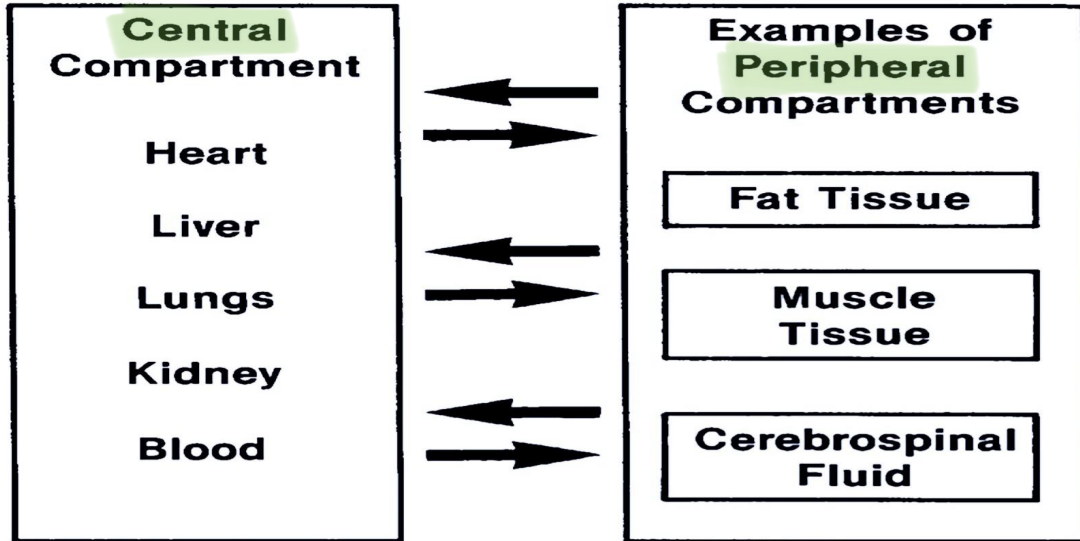
* One-compartment, two-compartment, or multi- compartment model.

* 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
 - ^{۹۰٪} ^{معن دراستی} 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

Mathematical review

- 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 $\mu\text{g}/\mu\text{L}$.
- Calculate the MW of the drug?
- Units of concentration in M?

- 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? *Answer: According to mass (amount)*

$$\frac{\cancel{\text{mg}}}{\cancel{\text{mL}}} * \frac{1\cancel{\text{g}}}{10^3\cancel{\text{mg}}} * \frac{10^3\cancel{\text{mL}}}{1\cancel{\text{L}}} = \frac{\text{g}}{\text{L}}$$

Logarithms

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

$$e \approx 2.718$$

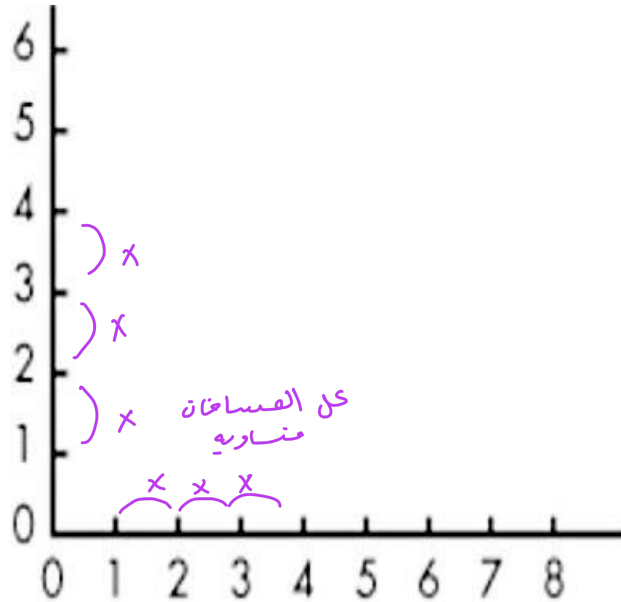
$$\underline{2.303 \log N = \ln N}$$

- A logarithm does not have units = dimensionless

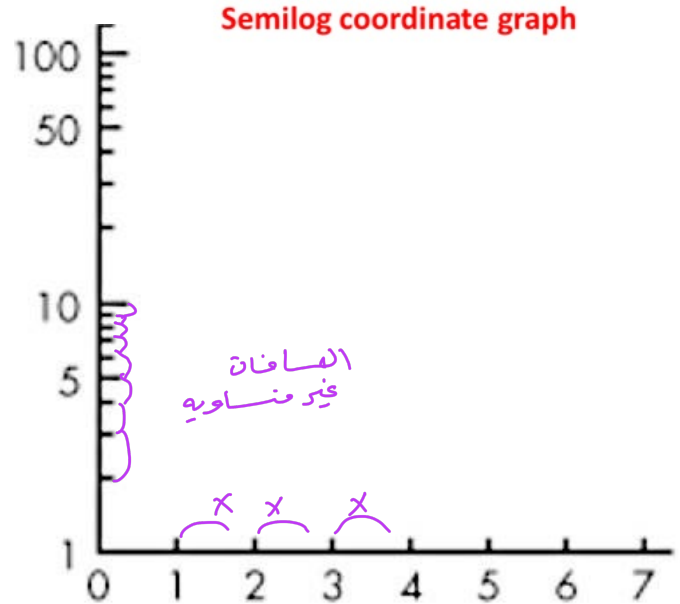
PARAMETER	SYMBOL	UNIT	EXAMPLE
Rate $\rightarrow \frac{mg/L}{hr} \left(\frac{mg}{L} + \frac{1}{hr} \right)$ $mg/L \cdot hr \rightarrow mg \cdot hr^{-1} / L$	$\frac{dD}{dt}$	$\frac{Mass}{Time}$	mg/hr
	$\frac{dc}{dt}$	$\frac{Concentration}{Time}$	$\mu g/mL \cdot hr$
Zero-order rate constant	k_0	$\frac{Concentration}{Time}$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

AUC $\mu g \cdot hr/mL$

Conc. \times Time
 $\frac{mg}{L} \times hr$
 $\frac{mg}{L \cdot hr}$



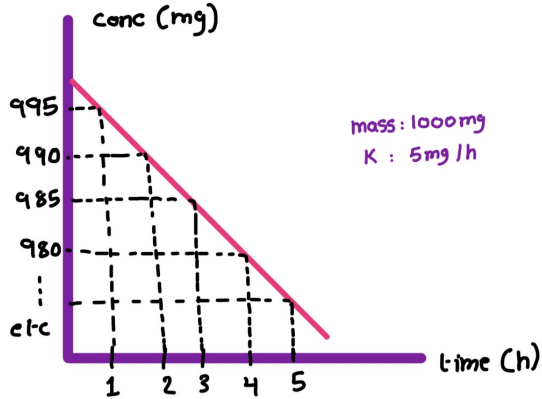
Rectangular coordinate graph



• **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

Zero order reaction



عقدار تناقص ثابت لا يعتمد على :

① الكمية المعطاة (dose)

② الكمية القبل

First order reaction

* بينما هون كميّه التناقص غير ثابتة وتعتمد على ال Dose

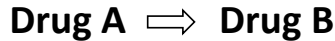
* مثال :

لو مقدار التناقص $10\%/h$ / $mass: 100\text{mg}$

Time	Conc.
Zero	100
1h	90 $(100 - (100 * 10\%))$ $(100 - 10)$
2h	81 $(90 - (90 * 10\%))$ $(90 - 9)$
3h	72.9 $(81 - (81 * 10\%))$

Rates and Orders of Reactions

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



- 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

$$-dA/dt = k * A^n \rightarrow \text{order}$$

$n \rightarrow$ determine the rate of the reaction

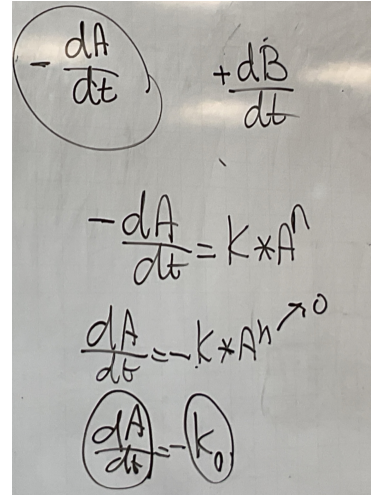
* Zero order reaction

- Drug A is decreasing at a constant time interval t
 $n=0$

$$\begin{aligned}dA/dt &= -k_0 * A^0 \\dA/dt &= -k_0\end{aligned}$$

k_0 : is the zero-order rate constant

Unit of k_0 : mass/time (e.g. g/h)



$$dA/dt = -k_0$$

→ Rearrange

→ Integrate

$$A = -k_0 t + A_0$$

$$y = ax + b$$

$$\text{Conc.} = -k_0 t + C_0$$

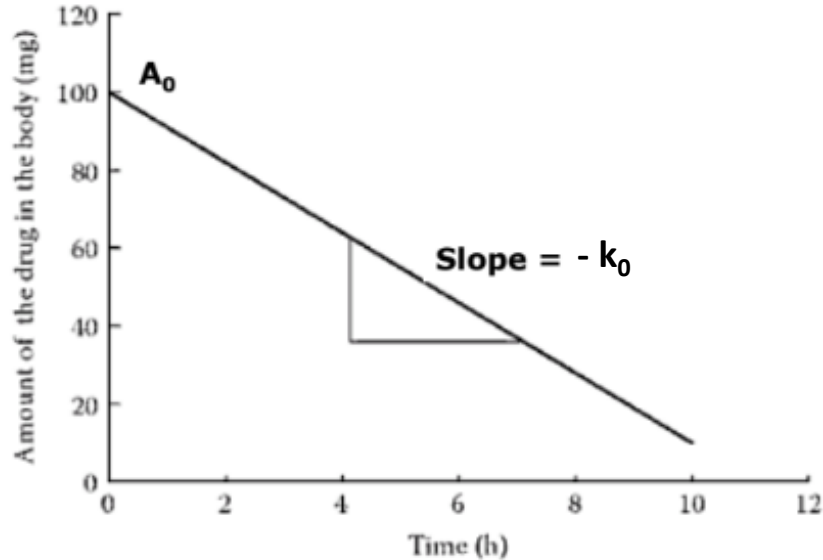
(conc. at time zero)

A: Amount (mass) in mg/g ---etc

k₀: elimination constant

A₀: Amount of drug at time zero

$$A = -k_0 t + A_0$$



Concentration $\rightarrow C = -k_0 t + C_0$

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. *what time was it when $C = \frac{C_0}{2}$*

- Zero-order half-life:

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

الاشتقاق

$$\begin{aligned}
 A &= -k_0 t + A_0 \\
 0.5 A_0 & \quad \quad \quad t_{1/2} \\
 0.5 A_0 &= -k_0 t_{1/2} + A_0 \\
 -k_0 t_{1/2} &= 0.5 A_0 - A_0 \\
 -k_0 t_{1/2} &= -0.5 A_0 \\
 t_{1/2} &= \frac{0.5 A_0}{k_0}
 \end{aligned}$$

- 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 **is NOT constant**

Zero-Order Reactions: example

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

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

* لو بيري V_d

$$C = \frac{mg}{V_d(L)} \rightarrow V_d = \frac{mg}{C}$$

$$= \frac{1000}{100}$$

$$\underline{\underline{V_d = 10 L}}$$

الحل

10 mg → 4h
 ? ← 1h
 1h = 2.5 mg
 إذا كمية الناقص
 ثابتة 2.5 mg/L
 Zero order

في حالة صاء السؤال
 العنود الثاني يعنى تركيز

$$A = -k_0 t + A_0 \xrightarrow{\text{conc.}}$$

$$Y = -2.5X + 100$$

في حالة كان العنود
 الثاني Amount

$$Y = -2.5X + 1000$$

الاعداد غير متساوية

Zero-Order Reactions: example

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

✓

- What is the rate constant?

$$C = -k_0t + C_0$$

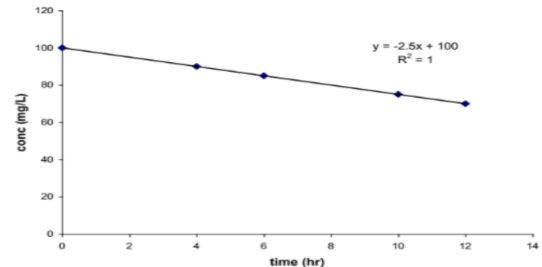
$$y = -Kx + C_0 \rightarrow (x, y) = (4, 90)$$

$$90 = -K(4) + 100$$

$$-10 = -4K \rightarrow K = \frac{10}{4} = 2.5 \text{ mg/h}$$

OR

10 mg \rightarrow 4h
? \leftarrow 1h
1h = 2.5 mg
إذا كمية الناقص
2.5 mg / L

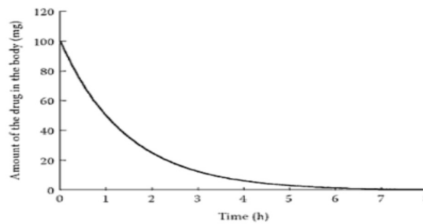


Zero-Order Reactions: example

صاف

- 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:

$$dA/dt = -k * A^1_{\text{remaining}}$$

- 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:

$$\text{بعد التناول} \longrightarrow A = A_0 e^{-k^* \cdot t}$$

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:

$$\begin{aligned} \ln A &= \ln A_0 - k^* \cdot t \\ \ln A &= \ln A_0 - kt \\ \frac{\ln A}{y} &= \frac{-kt}{x} + \frac{\ln A_0}{\text{const.}} \\ \underline{y} &= \underline{ax} + B \end{aligned}$$

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

- $dA/dt = -k \cdot A$

- $A = A_0 \cdot e^{(-kt)}$ [e]

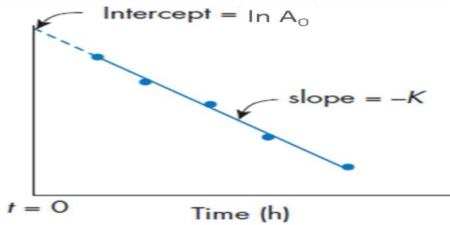
- $\ln A = -k \cdot t + \ln A_0$ [ln]

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

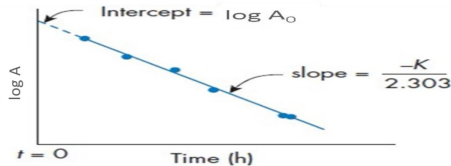
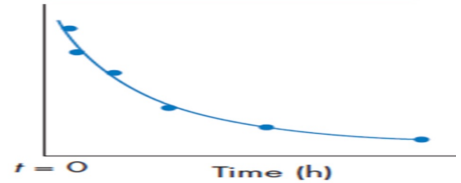
- $\log A = - (k \cdot t / 2.303) + \log A_0$

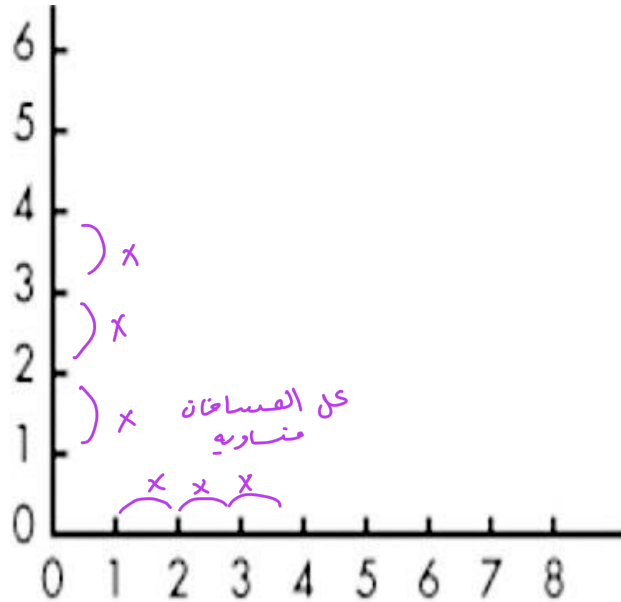
- A, k, A0:

$$\ln A = -k \cdot t + \ln A_0$$

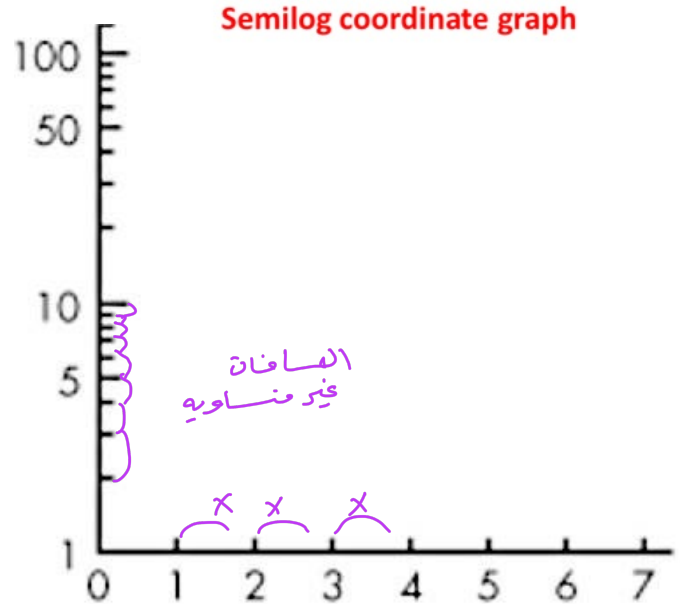


$$A = A_0 \cdot e^{(-kt)}$$





Rectangular coordinate 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

cont

$$dC/dt = -k \cdot C$$

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

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

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

• **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:

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

- $t_{1/2}$ is a constant. No matter what the initial A or C

- The time required for the amount to decrease by one-half **is CONSTANT**

Handwritten derivation of the half-life formula on a whiteboard:

$$\ln A = \ln A_0 - kt$$
$$\ln(0.5A_0) = \ln A_0 - kt_{1/2}$$

A curved arrow indicates the subtraction of the second equation from the first.

$$kt_{1/2} = \ln A_0 - \ln(0.5A_0)$$
$$kt_{1/2} = \ln \frac{A_0}{0.5A_0}$$
$$t_{1/2} = \ln 2 / k$$

Example:

$$\ln A = \frac{-1t}{-k} + 10 \quad \text{---} \quad -1t = -kt \rightarrow \therefore k = 1 \frac{1}{\text{hr}}$$
$$k = 1/\text{hr}$$

a) 1 hr

✓ b) 1 hr⁻¹

c) 2.303 hr

d) 2.303 hr⁻¹

e) None

$$\frac{-k}{2.303} = 1$$
$$k = 2.303 \text{ hr}^{-1}$$

حد غلط
استرانی n استی 10

Zero

$$\frac{dA}{dt} = -K_0$$

$$A = -K_0 t + A_0$$

C C₀

↙ Not constant

$$t_{1/2} = \frac{0.5 A_0}{K_0}$$

First

$$\frac{dA}{dt} = -K_0 A_1$$

(remaining)

$$\ln(A) = \underbrace{-Kt}_{\text{slope} = -K} + \ln(A_0)$$

$$\log(A) = \frac{-Kt}{2.303} + \log A_0$$

slope = $\frac{-K}{2.303}$

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

constant