

The background of the slide is a dense, repeating pattern of various colorful pills and capsules. The colors include orange, green, pink, blue, purple, red, yellow, and teal. The shapes are diverse, including round tablets with white lines, oval capsules, and some with distinct markings.

PHARMACOKINETICS

Saef dawwas

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.

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.

صوت عملياً كثير بين تستخدم
للي عند قهر امراض كبد
(metabolism بتأثر) ومرض الـ ICU

Basic Pharmacokinetics and Pharmacokinetic model

انها بتغير

- 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.

ما يعرف بالضبط شو يصير بالجسم عشان هيقا
بنظرة فرضيات (models)

- 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.

صحيح كده

PK models

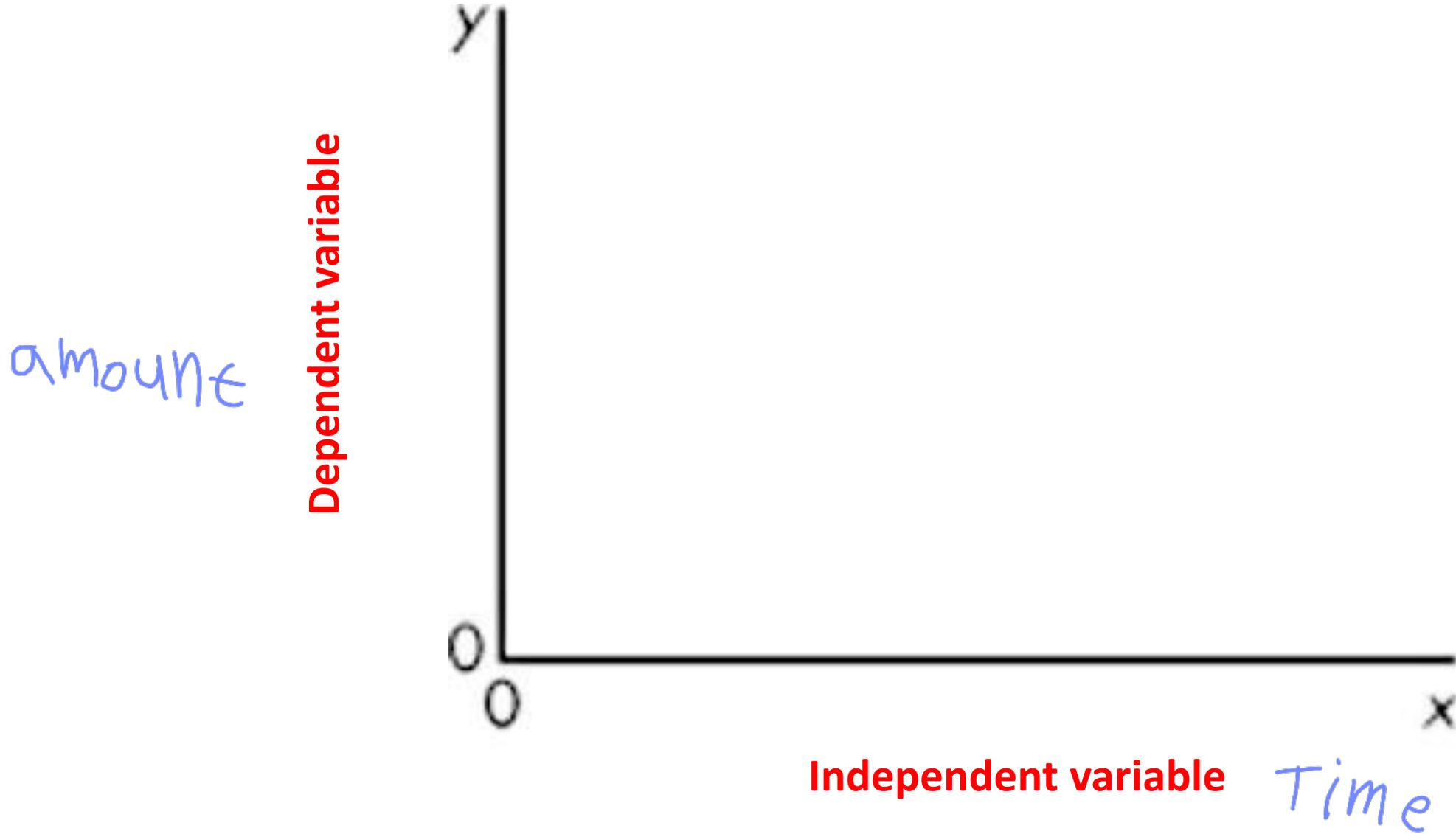
- **Model**: a hypothesis using mathematical terms to describe quantitative relationships concisely.
- **Pharmacokinetic parameter**: ^{مقاييس} is a constant for the drug that is estimated from the experimental data. For example, estimated pharmacokinetic parameters such as k depend on the method of 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

ببساطنا للتوقع كمية الدواء على اي وقت نجنا



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.

حسب كيف بقسم الجسم (على اساس توزيع الدم وعدد مرات انتقاله)

- 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.

ادوات زيادات الـ compartment comparison بتزيد الـ boxes

المتشابهين مع بعض

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

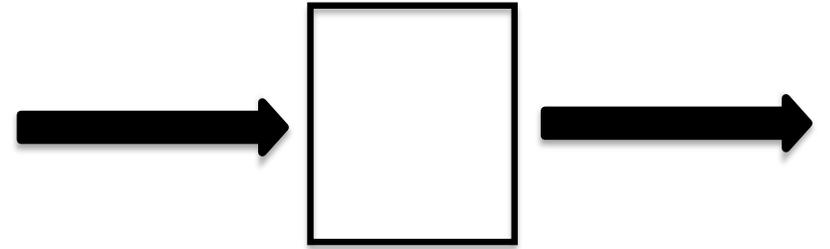
- * The [drug] in the compartment for a given dose is determined by :

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

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

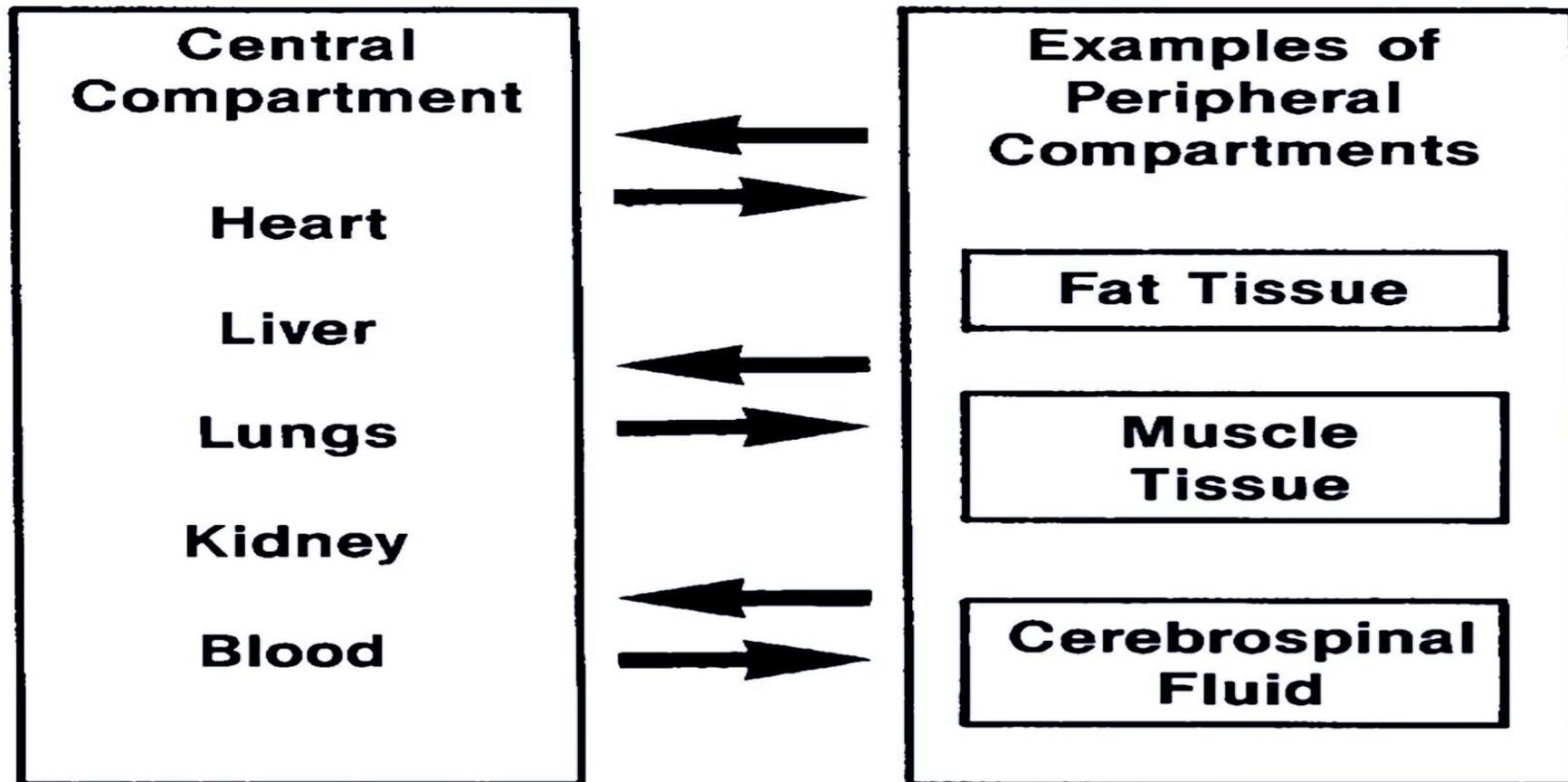
- * One-compartment, two-compartment, or multi-compartment model.

- * 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,

احتمالاً بنظري
عن نظام ثابت

لأنها نظرياً لها معدلات

- Most PK models assume

كل مكان توزع كمية نفسها

- instant homogeneous distribution of drug within each compartment "well-stirred"

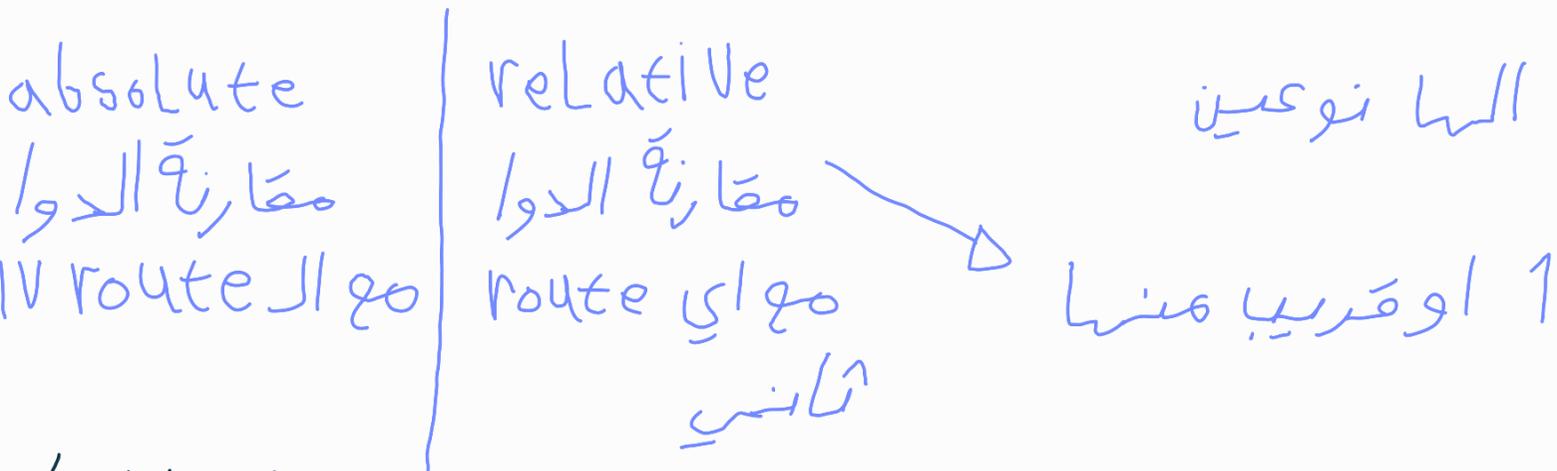
- and elimination rate constant does not change over time

من ساعة لساعة نفسه



- Model parameters (e.g. V and k) are determined experimentally from a set of drug concentrations collected over various times
- \uparrow parameters \rightarrow \uparrow complexity of the model
 - \rightarrow \uparrow data needed
- Compartmental PK models are useful esp. when little information is known about the tissues

Bio availability : كمية توافر الدواء في الأنسجة



براءة الاختراع

patency : كل اشياء عملتوا الشركة لما صنعت الدواء

relative bioavailability يشوفوا انو احسن من ال FDA يشوفوا انو احسن من ال بال سوق او لاء. عشان يعطوا براءة اختراع

individualizing : تعديل الدواء لمريض محدد

comparment model : يعتبر الجسم نظام واحد one box

هي المرضية الوحيدة التي اكثر اشياء بتفسر الي بصير جوا الجسم لل kinetic و ابيط نظرية بتؤخذ عينات من الدم بفترات مختلفة

كيف يعني انو الجسم one box ؟
يعني الجسم عبارة عن تزان واحد للدم وفي
اماكن high fusion للدم واماكن Low

Mathematical review

- Do you know?/ Can you?
- The units used usually for concentration? *mass / volume*
- 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?

1g \rightarrow 1000 mg

1L \rightarrow 1000 mL

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? *1 L if the mg stay 0,6*

- For the following equation: ($y=1.8x+2$)

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

b. If $x = 0.5$, what is y ?

c. If $y = 4.6$, what is x ?

cont

$$\text{slop} = \frac{\Delta y}{\Delta x} =$$

- What is the slope of the line that connects the following two points?
- 1) $x=5, y=8.6$
- 2) $X=0.6, y=4.5$
- Solve the following equations for x :
 - a. $\log x = 0.95$ $10^{0.95}$
 - b. $e_x = 0.44$ $\ln 0,44$
 - c. $\ln x = 1.22$ $e^{1.22}$

$$e = 2,719$$

Basic exponent laws

- Expression: $N=b^x$

Laws of Exponents

$$a^x \cdot a^y = a^{x+y}$$

$$(a^x)^y = a^{xy}$$

$$\frac{a^x}{a^y} = a^{x-y}$$

$$\frac{1}{a^x} = a^{-x}$$

$$\sqrt[y]{a} = a^{1/y}$$

Example

$$10^2 \cdot 10^3 = 10^5$$

$$(10^2)^3 = 10^6$$

$$\frac{10^2}{10^4} = 10^{-2}$$

$$\frac{1}{10^2} = 10^{-2}$$

$$\sqrt[3]{a} = a^{1/3}$$

Logarithms

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

$$e \approx 2.718$$

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

- A logarithm does not have units = dimensionless

Laws of Logarithms

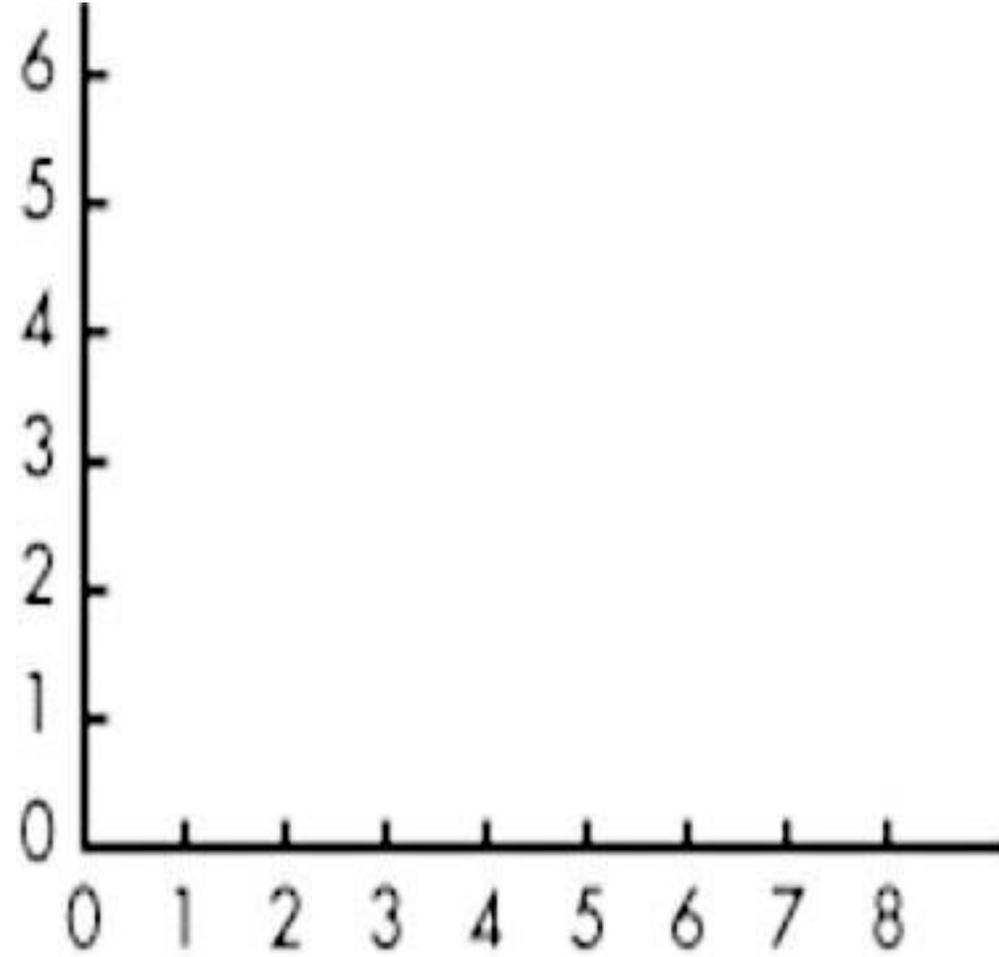
$$\log ab = \log a + \log b$$

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

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

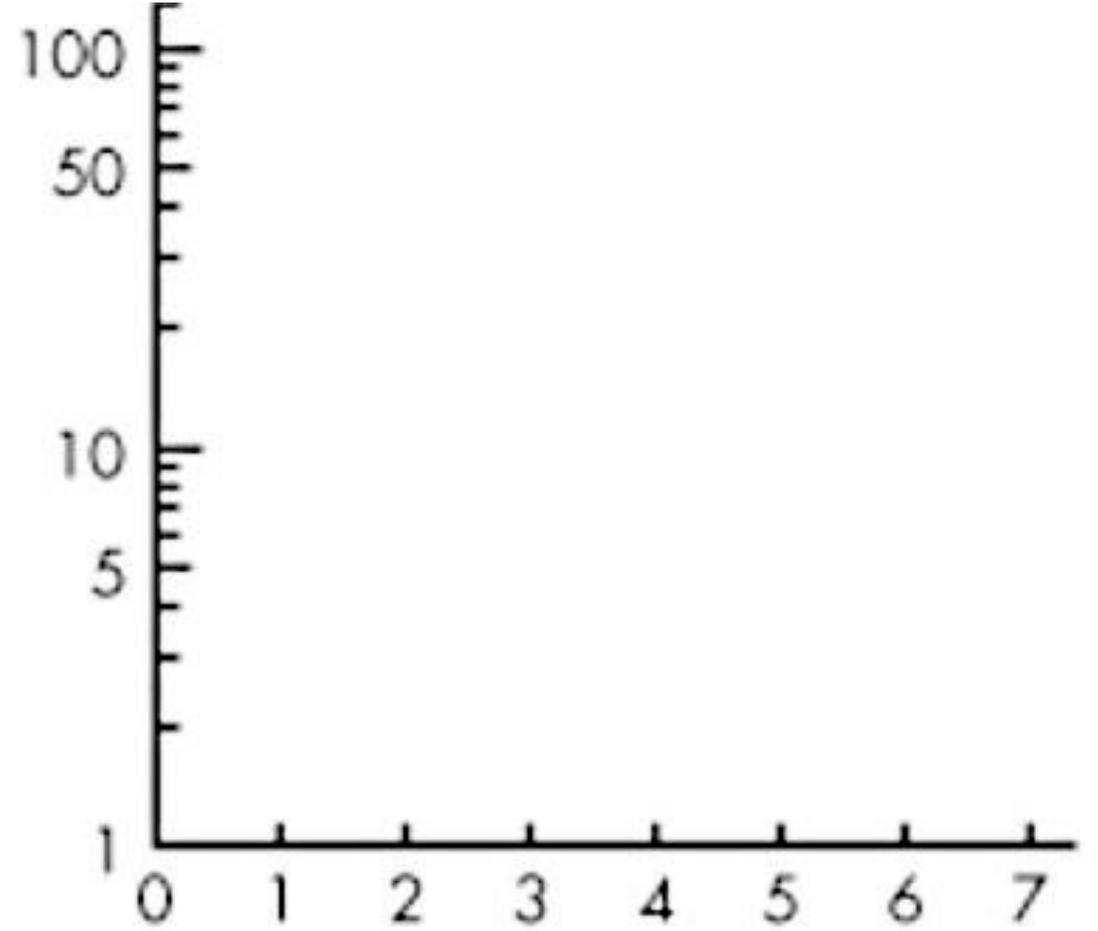
$$-\log \frac{a}{b} = +\log \frac{b}{a}$$

- Your calculator \rightarrow log, ln, anti-log and anti-ln



Rectangular coordinate graph

Linear
مترق الوحدات الثابتة



Semilog coordinate graph

العكس

cont

- Straight line eqt.

$$\bullet y = ax + b$$

- Slope? intercept?
- For a given straight line \rightarrow calculate slope
(on rectangular or semilog graph)

- **REMEMBER:**

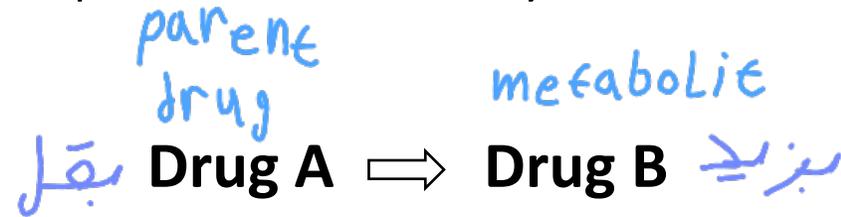
In semilog graphs : the y values are plotted on a logarithmic scale **without** performing actual logarithmic conversions, whereas the corresponding x values are plotted on a linear scale

PK units

PARAMETER	SYMBOL	UNIT	EXAMPLE
Rate	$\frac{dD}{dt}$	$\frac{\text{Mass}}{\text{Time}}$	mg/hr
	$\frac{dc}{dt}$	$\frac{\text{Concentration}}{\text{Time}}$	$\mu\text{g/mL hr}$
Zero-order rate constant	k_0	$\frac{\text{Concentration}}{\text{Time}}$	$\mu\text{g/mL hr}$
		$\frac{\text{Mass}}{\text{Time}}$	mg/hr
First-order rate constant	k	$\frac{1}{\text{Time}}$	$1/\text{hr}$ or hr^{-1}
Drug dose	D_0	Mass	mg
Concentration	C	$\frac{\text{Mass}}{\text{Volume}}$	$\mu\text{g/mL}$
Plasma drug concentration	C_p	$\frac{\text{Drug}}{\text{Volume}}$	$\mu\text{g/mL}$
Volume	V	Volume	mL or L
Area under the curve	AUC	Concentration x time	$\mu\text{g hr/mL}$
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 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:

$$-dA/dt$$

$$d = \Delta$$

- 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.

كيفية التناقص ثابتة

Zero order reaction

مع الوقت Linear

• 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 constant time interval t
n = 0

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

k₀: is the zero-order rate constant

elimination rate constant

Unit of k₀: mass/time (e.g. g/h)

ثابتة
لكل دواء
لحالة

$$dA/dt = -k_0$$

→ Rearrange

→ Integrate

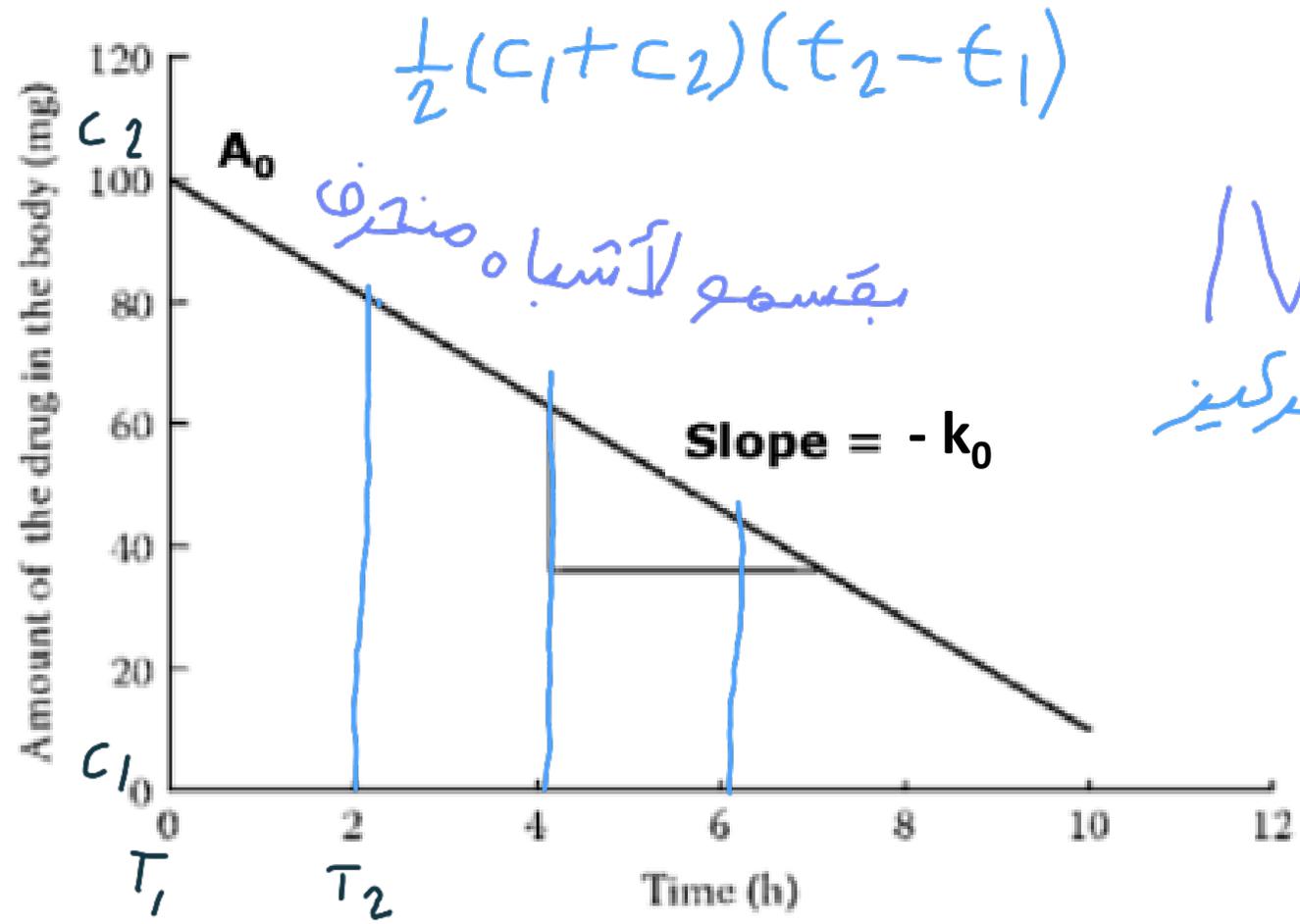
$$A = -k_0 t + A_0$$

A: y

k_0 : Slope x

A_0 : intercept b

$$A = -k_0 t + A_0$$



IV
الكم تركيز
وقبل

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.
- 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 is NOT constant

Zero-Order Reactions: example

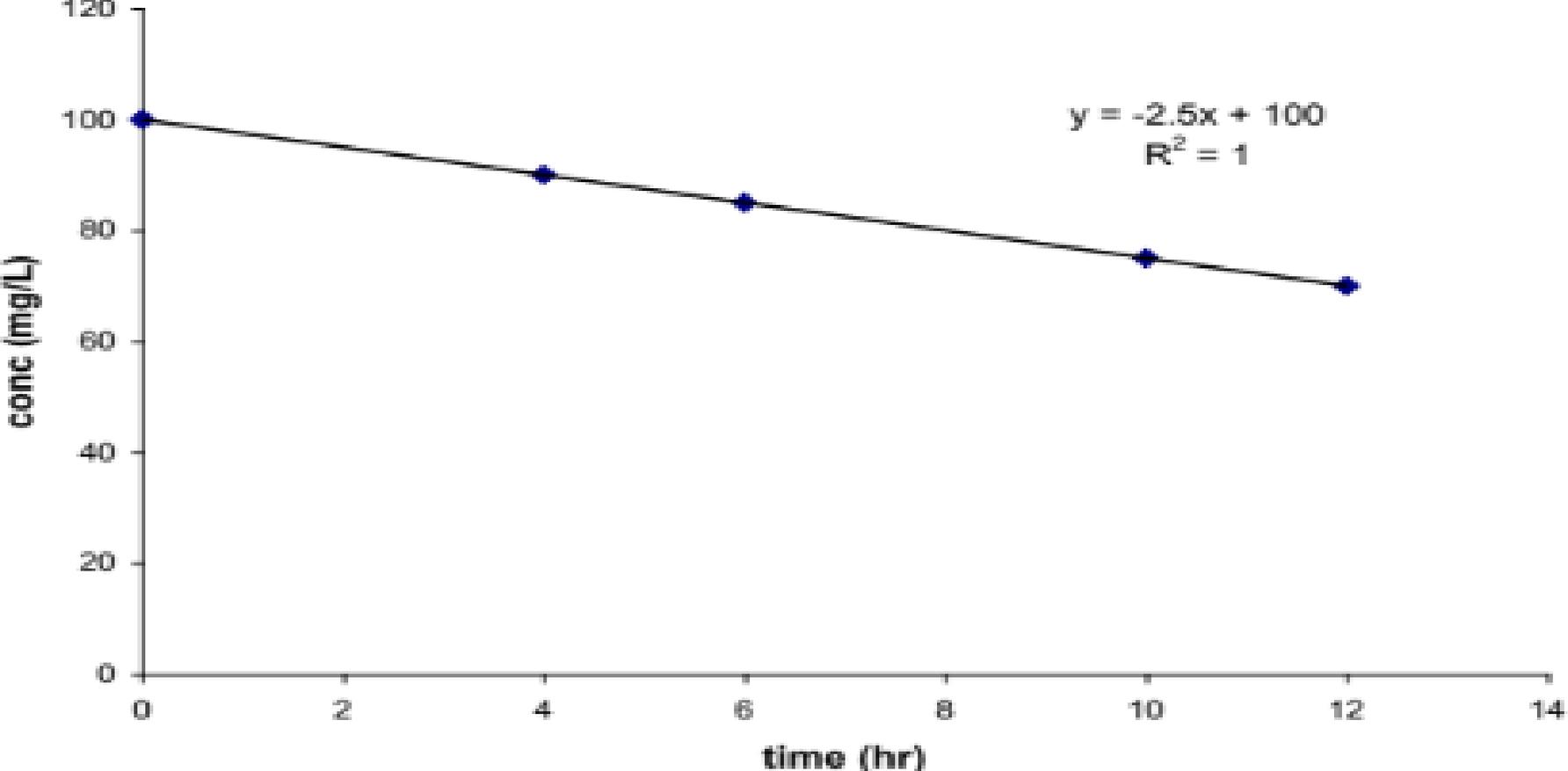
- The administration of a 1000 mg of drug X resulted in the following concentrations:

Time	Conc. (mg/L)
0	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:

$$dA/dt = -k \cdot A^1$$

- 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:

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

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

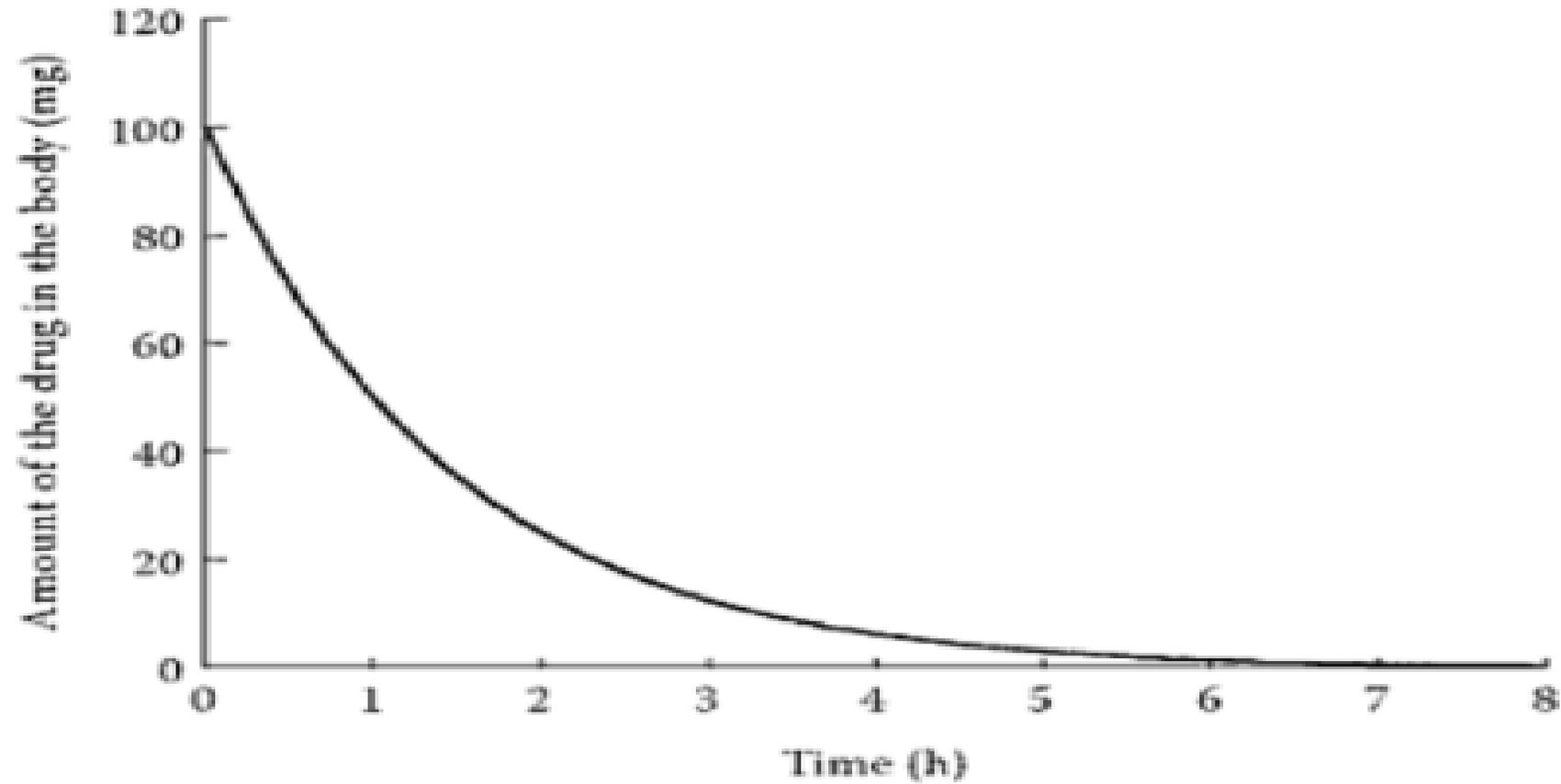
- $A = A_0 \cdot e^{(-kt)} \dots\dots\dots [e]$

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

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

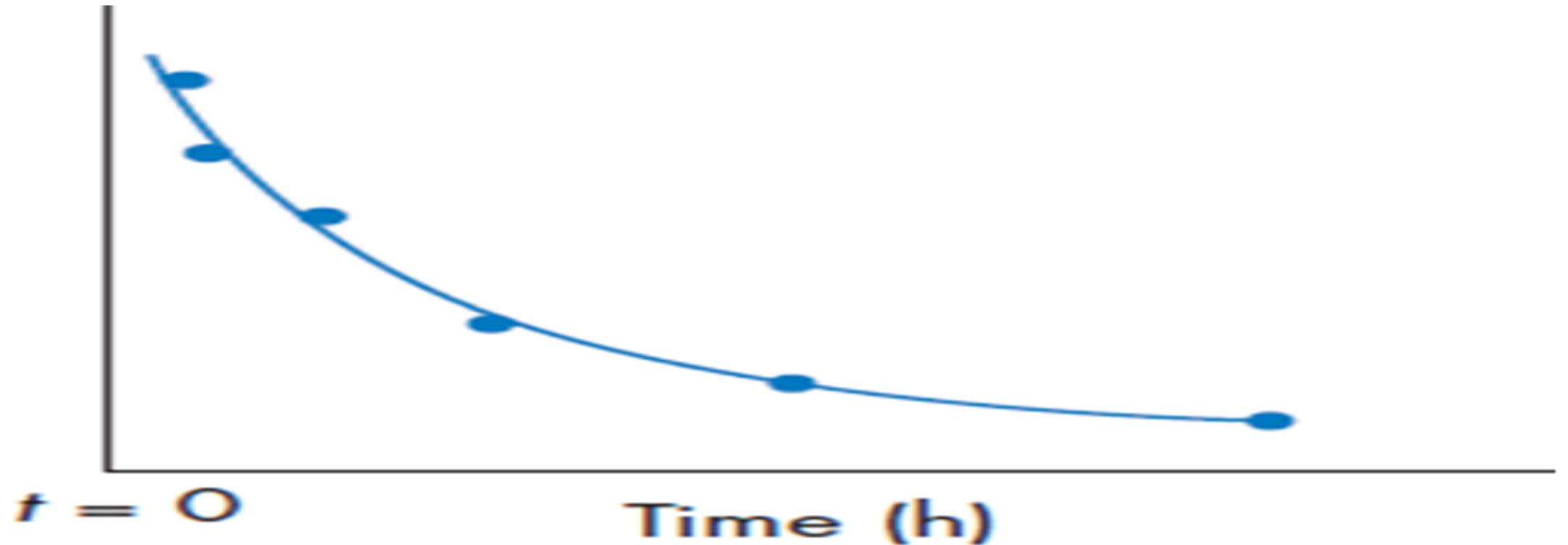
- **A, k, A0:**

Drug with first order kinetic



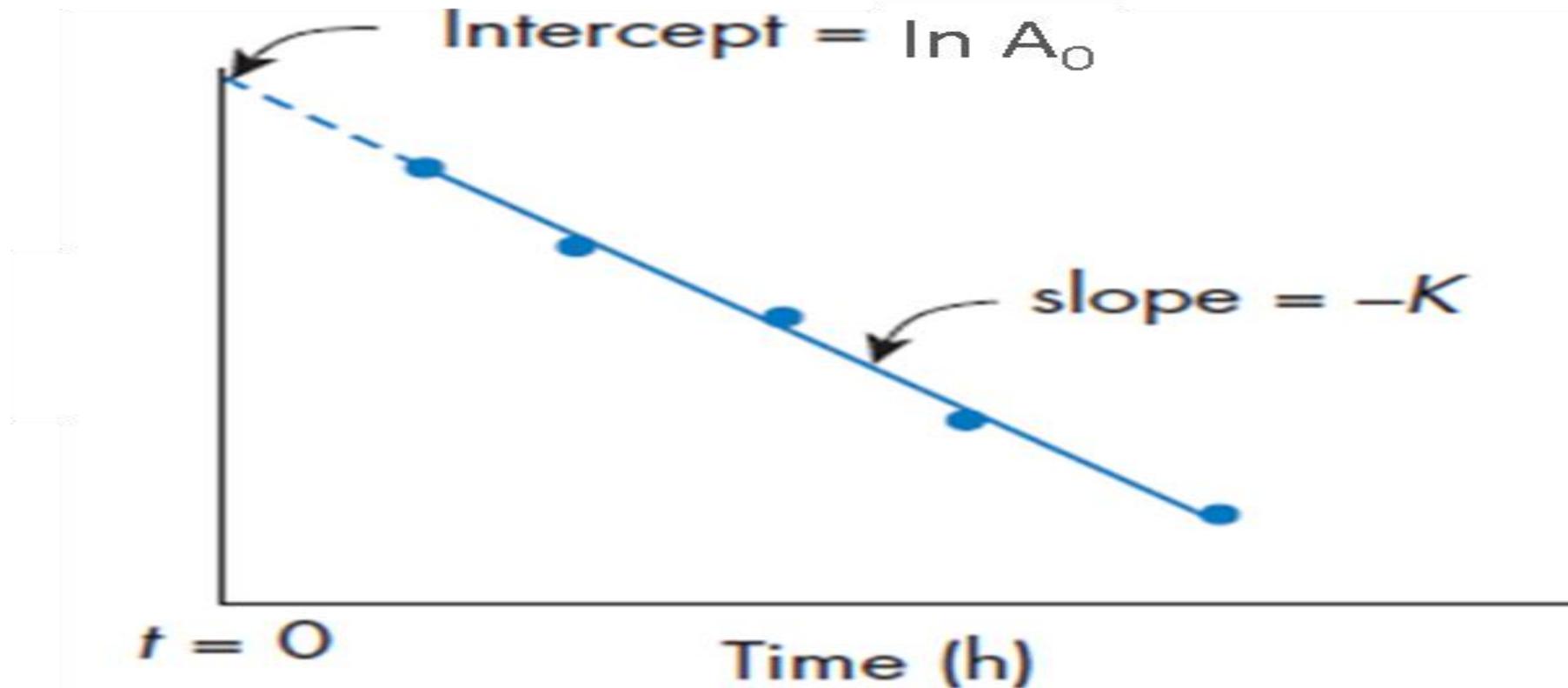
Rectangular coordinate graph

$$A = A_0 * e^{-kt}$$



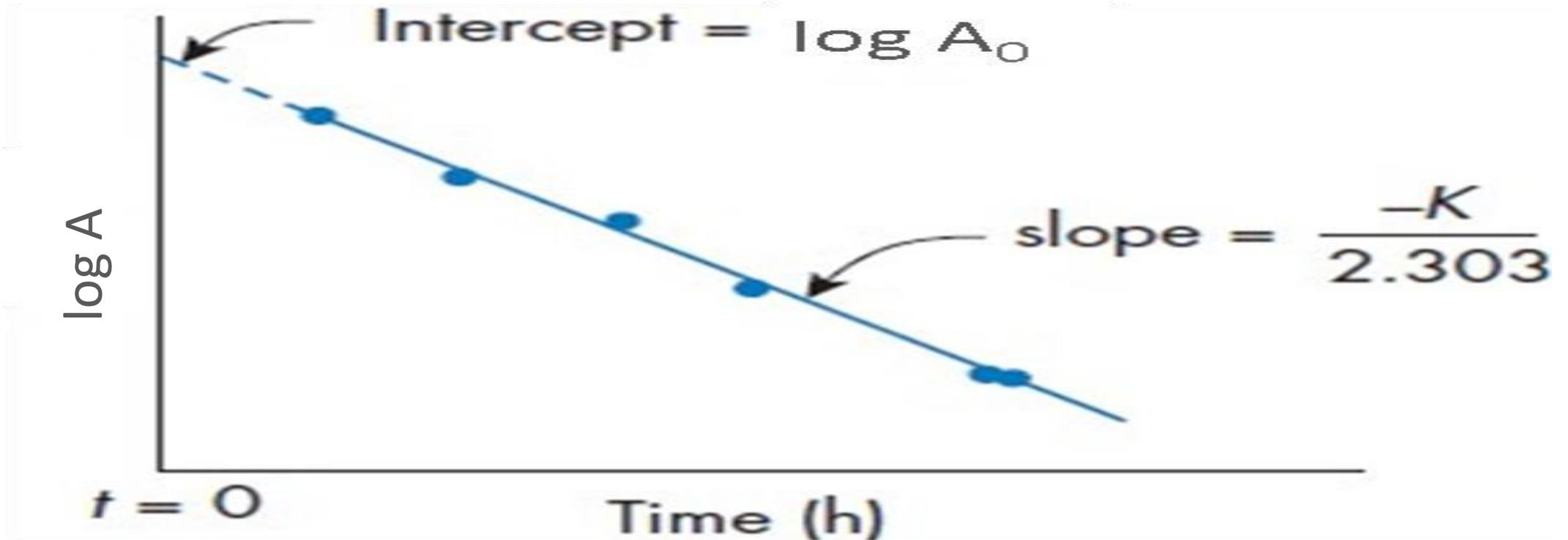
Semilog coordinate graph

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



Semilog coordinate graph

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



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**

متساوية
إذا الرسم exponential لا ينقذ، نطلع
صينا انشي فينقولها Linear (بنظيرها
رسمه Semi Log)

Drug A kinetic بيها

order هو للأدوية

zero يكون فقط لـ 1% من الأدوية

rectangle
first order يكون رسمها
Semi Log بيقولها

بالقانون A و C نفس الأثني

THANK YOU

ANY QUESTIONS?



آخر سلايد بالمحاضرة

بالتوفيق



Artery Academy