



MIRACLE Academy

حركة الدواء



لجان الرفعات

One compartment open model:
intravenous bolus administration

PK theory lec.3

One-compartment model

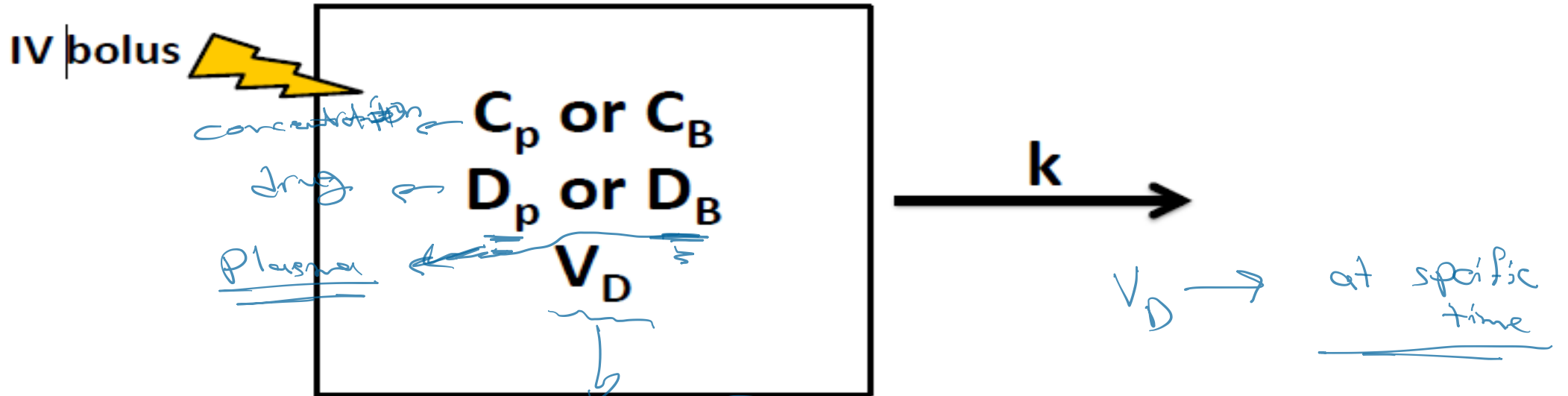
إذا أنت أعطيت دواء بـ intravenous dose

ليش blood في عنق مكونات
 WBC
 Interocyte blood cell
 Plasma



- IV bolus- One compartment model:

عشان فيك
 إذا روجت
 دose
 وحده لليتك
 هو نفس وحده
 blood
 plasma



Distribution

Open compartmental model

specific time ← $C_{*0} = \frac{X}{V_D}$ $\left[C_i = \frac{X_i}{V_D} \right]$

⊗ كما احكيك احسب V_D لترسم تكون

ال amount و concentration هما نفس الوقت
وهو بالامتحان يطلب من amount بعد ساعتين
وجايبك amount بعد ساعة بالخطية
فانتبه!

⊗ فالله اعلم انه يا ببحال مع dose و concentration و

يطلع هذا الدواء من compartment

K ← elimination rate constant

$$\left\{ C = \frac{\text{mass}}{V} \right\}$$

Cont,

IV → absorption ماخوذ

elimination ← { distribution + metabolism + excretion

- The simplest kinetic model that describes **drug disposition** in the body is to consider that the drug is injected all at once into a box, or compartment, and that the drug distributes **instantaneously** and **homogenously** (kinetically) throughout the compartment.

{ direct مباشر

rapid } { بمعدل طردي وليس متساوي } بتوزيع

- Drug elimination** also occurs from the compartment immediately after injection.

IV

One-compartment model assumptions

حصار، خاص الامتزاج
على طول خط
IV

Assumptions

• Rapid Mixing

drug is mixed instantaneously in blood or plasma.

• One compartment

Drug in the blood (plasma) is in rapid equilibrium with drug in the extravascular tissues.

• Linear Model

Drug elimination follows first order kinetics.

absorption

elimination
علاج
سواء

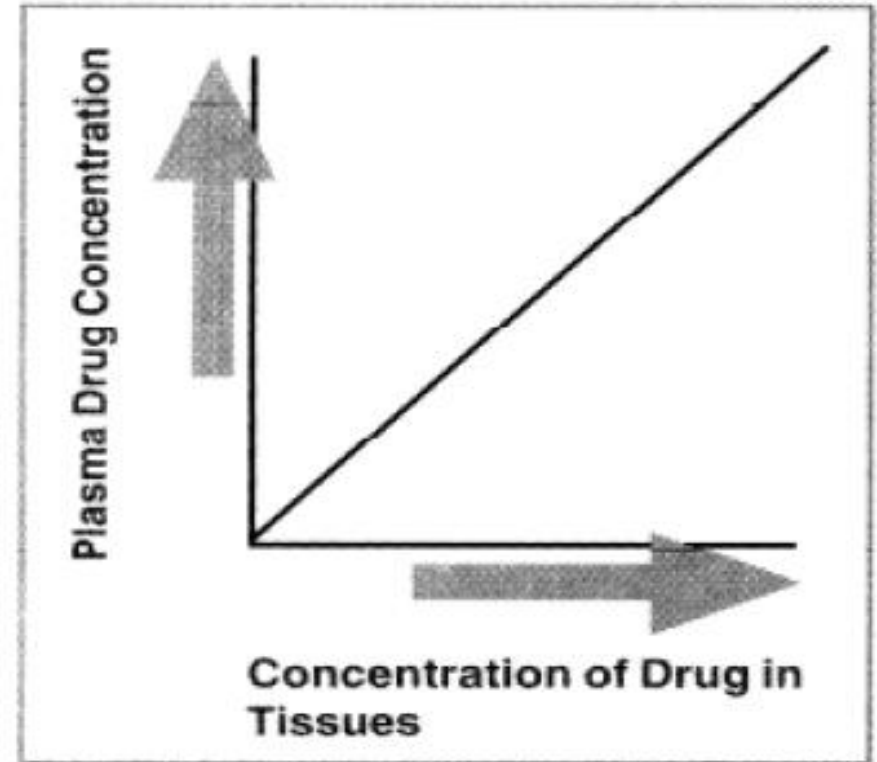


Figure 1.2. Relationship of plasma to tissue drug concentrations.

First order ← IV - bolus

Cont,
 أي تغير في concentration او - dose الكمية بتعطيلها لل drug
 بتوصل لل plasma رح يمس مباشرة تغير في concentration
 ب tissues / يدك تعرف انه كلما كانت الكمية الي بتعطيلها اكبر
 فالي رح يصل tissues أكثر

- Changes in the plasma drug concentration reflect changes in drug concentrations in other tissues.

Figure 1.3 is a simplified plot of the drug concentration versus time profile following an intravenous drug dose and illustrates the property of kinetic homogeneity.

- However, the plasma drug concentration does not equal the concentration at other sites but rather indicates how it changes with time.

مع الوقت Conc. or dose يتقل غالباً لكن بزيادة tissues

- Generally, if the plasma concentration of a drug is decreasing, the concentration in tissues will also decrease.

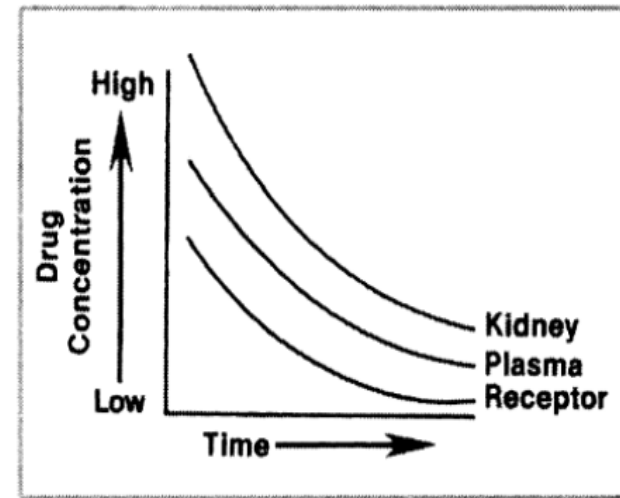


Figure 1.3. Drug concentration versus time.

Cont,

- The property of kinetic homogeneity is important for the assumptions made in clinical pharmacokinetics.
- It is the foundation on which all therapeutic and toxic plasma drug concentrations are established.
- That is, when studying concentrations of a drug in plasma, we assume that these plasma concentrations directly relate to concentrations in tissues where the disease process is to be modified by the drug (e.g., the central nervous system in Parkinson's disease or bone in osteomyelitis).
- This assumption, however, may not be true for all drugs.

Linear Kinetics (First order)

ممكن عن طريق kidney و liver

Elimination rate or change in concentration is proportional to the amount available for elimination.

افقد من active ingredients

حيز من kidney

و حيز من liver

Glomerular Filtration

Passive

-Tubular secretion

-Biliary secretion

-Biotransformation

Involve enzymatic processes (active)

برفع طاقت

kidney

liver

لیش بحکیمک ال elimination ممکن ب liver و ممکن ب kidney

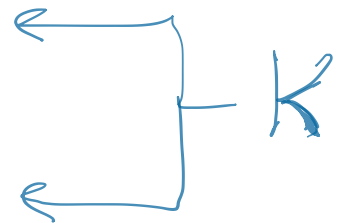
لکه بک متحاج بک ترکن هر کل elimination هر

بف طریق liver اذ اهر فطراً کل apparent صوره biotransformation

مخاتمه K هر لهر excretion بنسبه k_e

فال k_e بال kidney ← zero

metabolism k_m ← liver



excretion k_e ← kidney

elimination صوره $0.7 = k_m$

قطع $0.3 = k_c$ %30

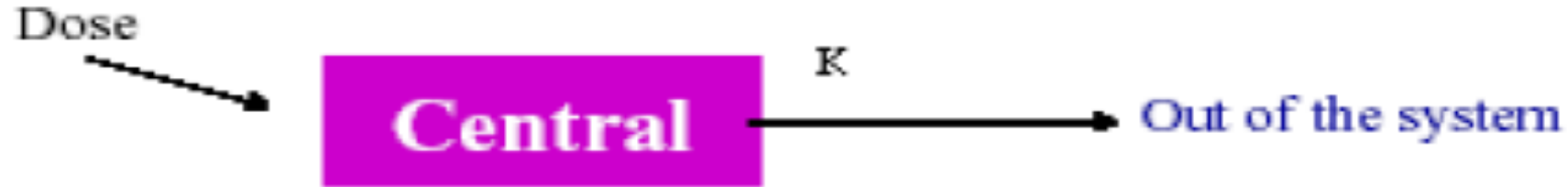
ب kidney ب اذ اهر کل

کل طور $\frac{zero}{k_m} = k_e$

* فک اذ اهر اهر $k_m = 0.7$ %70 elimination صوره

Cont,

1-Comp. Model: IV Bolus Dosing



X_t : the amount of drug remained in the compartment

K : first-order elimination rate constant (**OVERALL**)
(unit = time^{-1})

$$\text{Rate of elimination} = \frac{dX}{dt} = -KX$$

Amount
↓
Dose
Concentration

Exp. Glows
time

Elimination rate

Elimination rate is a first-order process



The elimination is dependent on the drug concentration or amount in the body

Elimination rate constant (k):

- 1st order rate constant
- Unit: 1/time (time⁻¹)
- $k =$ for all elimination processes = $k_e + k_m$ (Mainly)

$$k = k_e + k_m$$

k_e : 1st order rate constant of excretion

k_m : 1st order rate constant of metabolism

نتیجہ بریکورد > امجدات الحقیقہ 20

Cont,

- The rate of elimination from the compartment can be calculated as

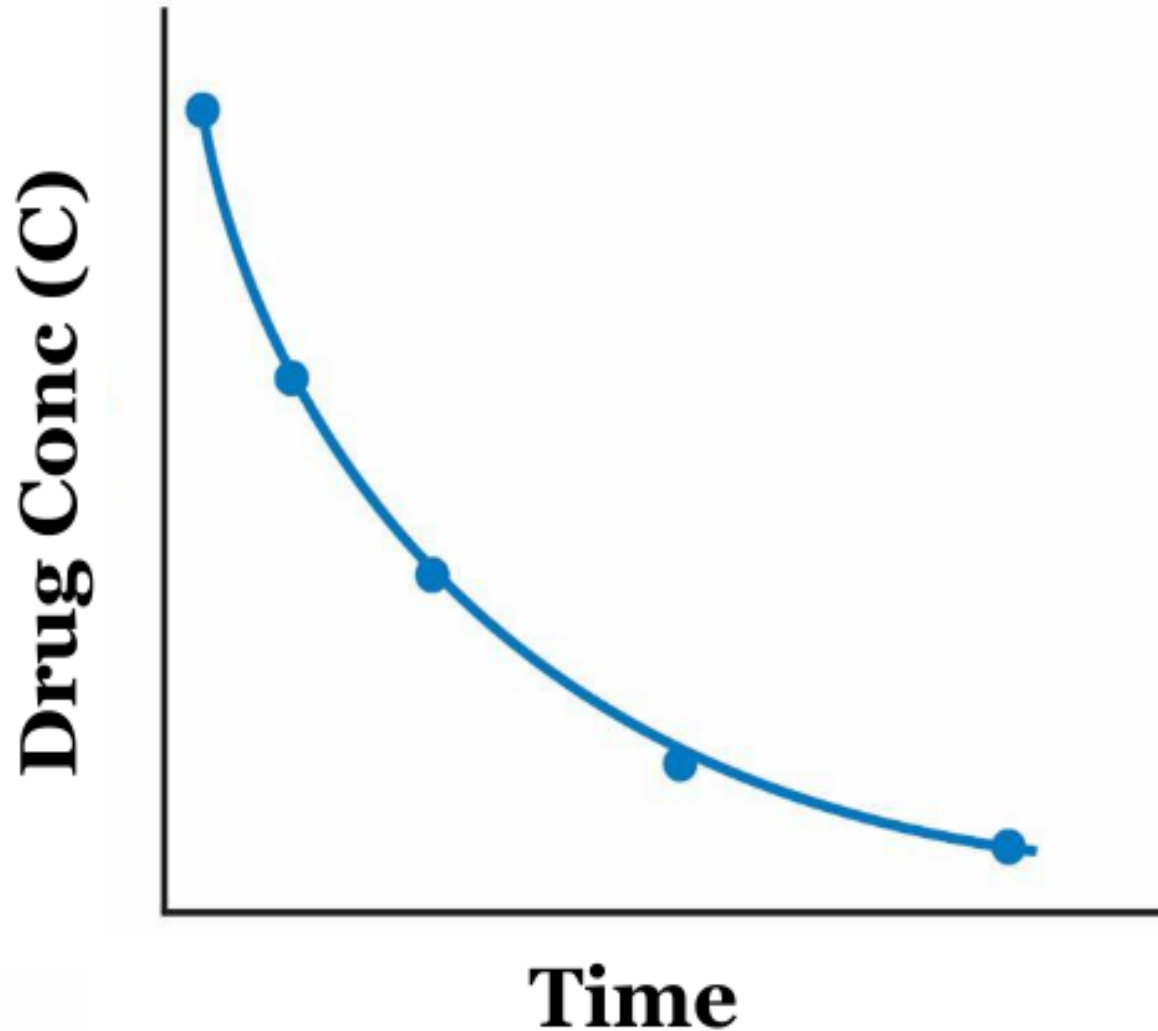
$$dD_B / dt = -k \times D_B$$

$$\ln D_B = -k \times t + \ln D_B^0 \dots \dots \dots [ln]$$

$$\log D_B = -\left(\frac{k}{2.303} \times t\right) + \log D_B^0 \dots \dots \dots [log]$$

$$D_B = D_B^0 \times e^{-kt} \dots \dots \dots [e]$$

One compartment open model



$$C = \frac{D}{V_d} e^{-K \cdot t}$$

C= concentration

D= dose

V_d: Volume of distribution → at specific time

K: elimination rate constant

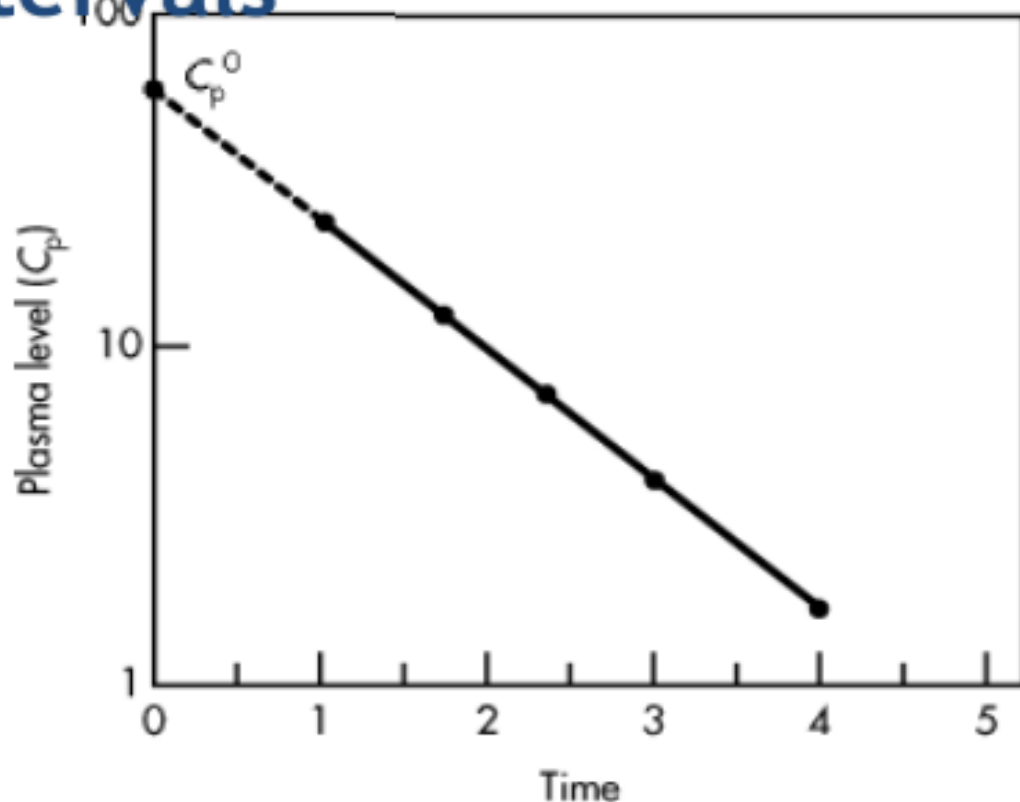
t: time

Calculation of concentration at different time intervals

- If the first plasma concentration is taken at t_1 instead of at zero and corresponds to plasma drug concentration C_1 , then C_2 is the concentration at time t_2 and t is set to $(t_2 - t_1)$ Then:

$$C_2 = C_1 * e^{-k(t_2 - t_1)}$$

$$\ln C_2 = \ln C_1 - k(t_2 - t_1) \quad -k = \frac{\ln C_2 - \ln C_1}{(t_2 - t_1)}$$



Source: Shargel S, Wu-Pong S, Yu ABC: *Applied Biopharmaceutics & Pharmacokinetics*, 5th Edition: <http://www.accesspharmacy.com>

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شرح لسلكه الى فوق بطلك انا ليست ما اصب بالقانون

Δt ← وهو احيانا الى بنقارن فيه $t_0 = 0$

في حلقه بنقارن على طول سوا t_0, t_1, \dots
فخص مصطلح اعمل Δt time

يعني بالارتعاع ما احييالك $A_{initial}$ بصيلا A بعد ساعات

و A بعد ثلاثة ساعات

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

لفترض ان

$$A_3 = A_1 * e^{-k(3-1)}$$

بدي اقلان
ال time الثالث والاول ←

* نفس مثال لسلكه لكن concentration

$$C_2 = C_1 * e^{-k(2-1)} \xrightarrow{\text{افضل}} \{ \ln C_2 = \ln C_1 - k(t_2 - t_1) \}$$

ومن حيث \ln طابع قانون k

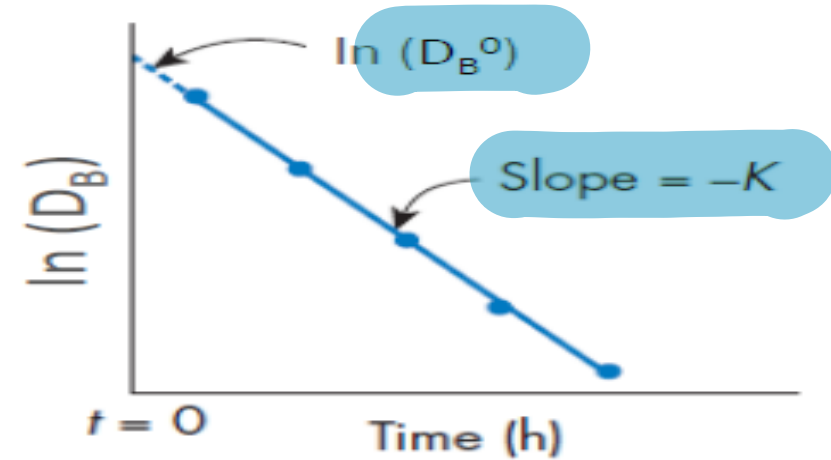
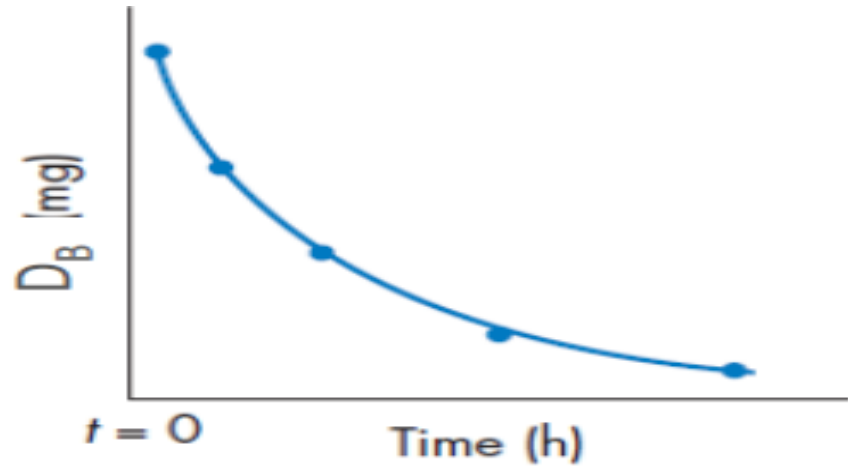
$$-k = \left[\frac{\ln c_2 - \ln c_1}{t_2 - t_1} \right]$$

أي هو مقياس فرق الصادات
عزق السينات \rightarrow Slope

$$\boxed{* \text{ Slope} = -k}$$

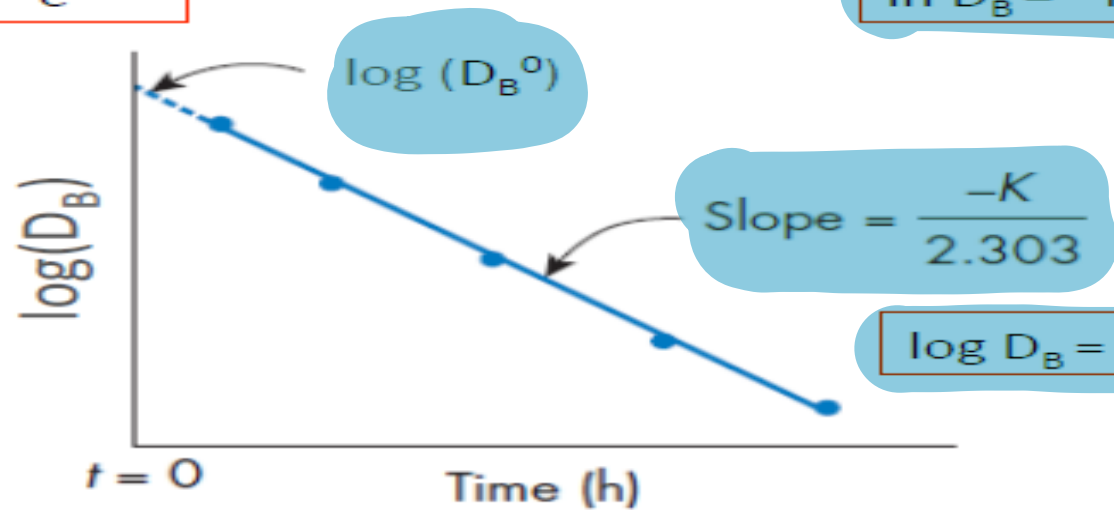
فالمساحة إذا ما أعطاك initial لا تتكلم بـ time أي معتد
أي بالساعة وهو تعودها كل واحد مكانه بشكل معتد

First order kinetic graphs



$$D_B = D_B^0 * e^{-kt}$$

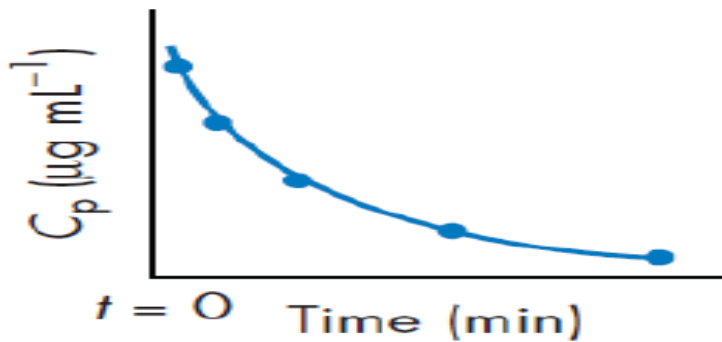
$$\ln D_B = -k*t + \ln D_B^0$$



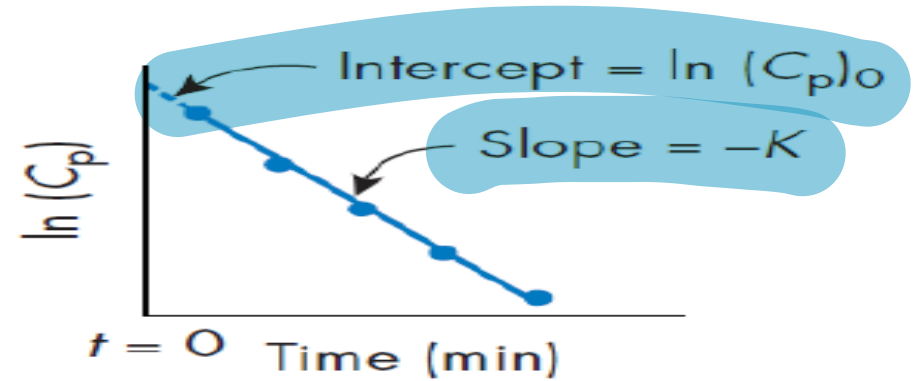
$$\log D_B = - (k*t/2.303) + \log D_B^0$$

- As we usually take samples from the plasma or blood \rightarrow then the results are in concentration units not mass units
- So we will have V_D and $C_p \rightarrow$

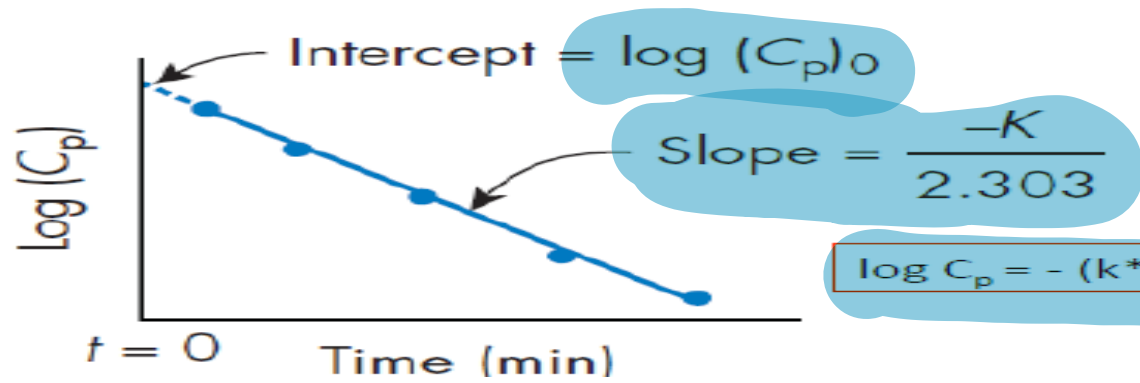
$$D_B = V_D * C_p$$



$$C_p = C_p^0 * e^{-kt}$$

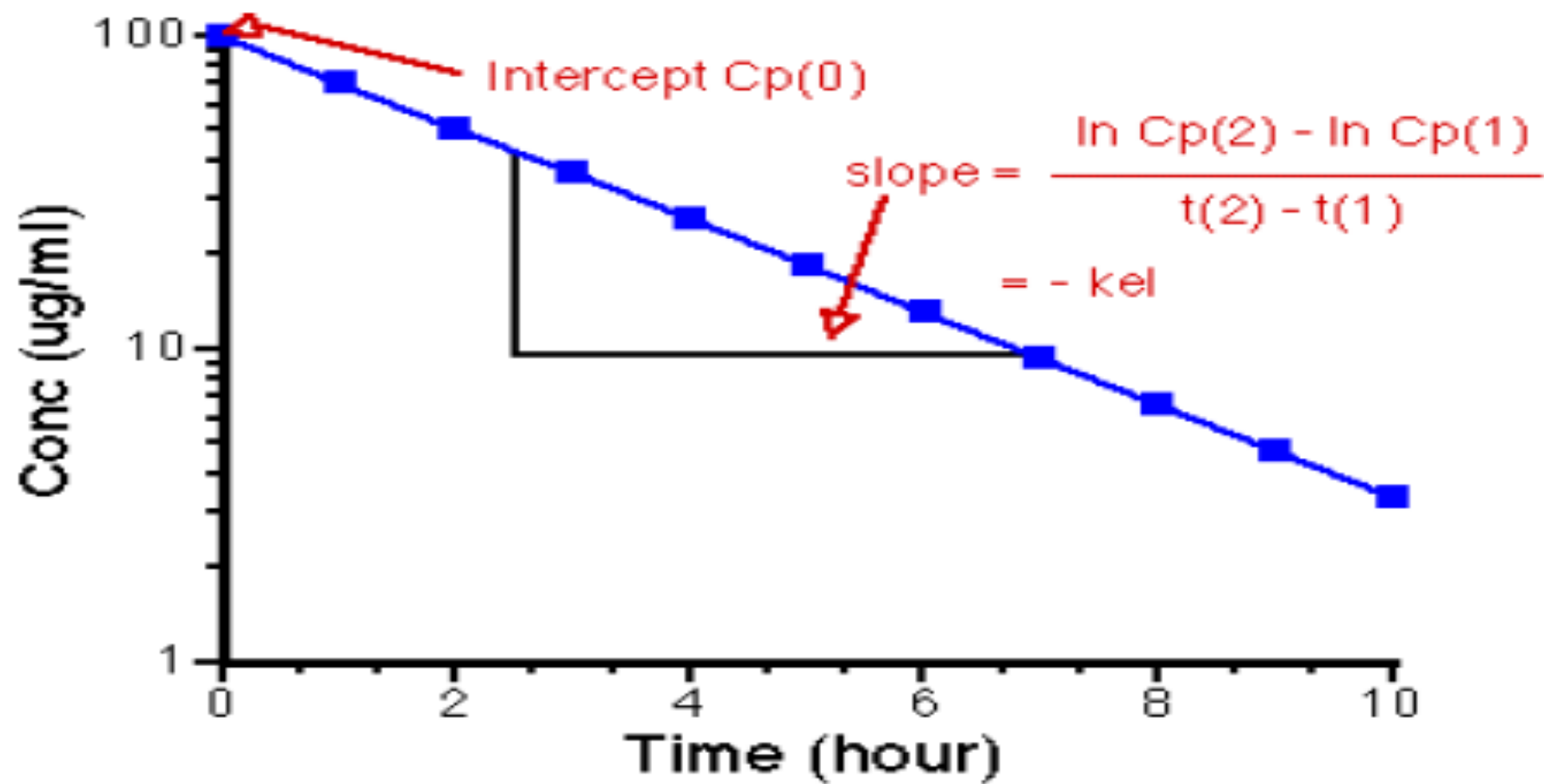


$$\ln C_p = -k*t + \ln C_p^0$$



$$\log C_p = - (k*t/2.303) + \log C_p^0$$

Determination of K



example

Practice questions

- Drug X has an elimination rate constant of 0.173 hr^{-1} , ^{*A amount*} 5 mgs of the drug were administered as an IV bolus. Calculate the following
- A) The drug amount after 2 hours
- B) The rate of reaction after 2 hours

① اول اسه بتفصل المعطيات بالسؤال

A)

بدر A بعين

اطلوع بالفرع الاول

على اى قوانين اسه ؟ على First order

$$A_e = A_0 * e^{-k * t}$$

$$A_2 = 5 * e^{-0.173 * 2}$$

B) rate of reaction →

$$\approx \frac{dx}{dt} = -k * A_0$$
$$\underline{\underline{-0.173 * 5}}$$

① بروح بتوف ورقتي فتبع القوانين

② بتوف قوانين First order ← rate of reaction

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

First order

هنول القوانين التلات اللى بتستخدم

قوانين التلاشي

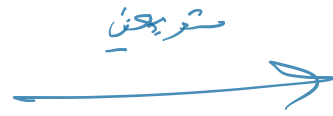
مباشرة

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

$$\frac{dA}{dt} = -k * A_0$$

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

ثابت ن
PK parameters



Constants
ثابت لخص الدواء والقياس التفاضل
ما لم يتم تحطيم جزيئات الدواء
او الحالة المرضية للشخص

Fundamental parameters in one compartment

- Apparent Volume of Distribution (V_d)
- Elimination rate constant (K)
- Elimination half life ($t_{1/2}$)
- Clearance (Cl)

Apparent Volume of Distribution (Vd)

ظاهري

حاجه لدرء و ليس للجسم



- This apparent volume of distribution is not a physiological volume. It won't be lower than blood or plasma volume but it can be much larger than body volume for some drugs.
- It is a mathematical factor relating the amount of drug in the body and the concentration of drug in the measured compartment, usually plasma:

①

من

at the same time

$$V_d = \frac{\text{AMOUNT of drug in the body}}{\text{CONCENTRATION in plasma}}$$

- Vd: A measure of the tendency of a drug to move out of the blood plasma to some other site.

خصائص الدواء الهيدروفيلية: الهيدروفيلية وفية هيدروفيلية hydrophilicity

وعنده protein binding ~~من~~ tissue binding كثير عالي هذا

يرفل فيه بالية جوا الغلية فكيفها، توزعه

$$421 = 28 + 10 + 46$$

هنا الكثير مسائل صويود بالجم

لكن distribution ممكن هو 600, 1000

خصائص خاصة الدواء من الجسم

Cont,

- Concentrations (mass per unit volume or amount per unit volume), not masses (mg or μg), are usually measured in plasma or serum (more often than blood).
- Therefore, a term is needed to relate the measured concentration (C_p) at a time to the mass of drug (X) at that time. This term is defined as the apparent volume of distribution (V).
- The apparent volume of distribution (V) is simply a proportionality constant whose sole purpose is to relate the plasma concentration (C_p) and the mass of drug (X) in the body at a time. **It is not a physiological volume**

$$V_d = \frac{\text{dose}}{\text{initial conc.}} = \frac{X_0}{C_0}$$

②

Factors Affecting Drug Distribution:

➤ Rate of distribution

✓ Membrane permeability

✓ Lipid Solubility

→ distribution ^{الانتشار} → hydrophilicity ^{طبيعا من انعام hydrophilicity}
لا فقط تكون نسبة lipid ^{لا فقط تكون نسبة lipid}

✓ pH - pKa (pH-partition theory for ionizable molecules)

✓ Blood perfusion of organs and tissues

➤ Extent of Distribution

✓ Plasma protein binding ↑

↑ → انتفاخ له أقل إنتل

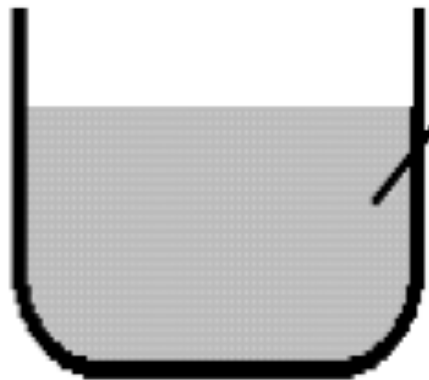
✓ Intracellular binding

~~~~~  
سكنيات <sup>سكنيات</sup> <sup>التي</sup> <sup>بجدها</sup> <sup>بمسرح</sup> هذا <sup>الاصلي</sup>

# Volume of distribution

**Definition:**  $V = \frac{\text{amount of drug in the body}}{\text{concentration measured in plasma}}$

**Drug concentration in beaker:**

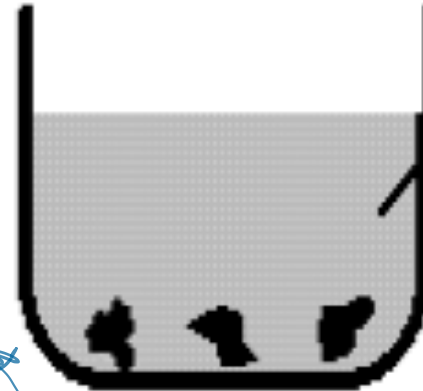


Dose = 10 mg  
 $C_p^0 = 20 \text{ mg/L}$   
Apparent  
Volume = 500 ml

كم نسبة مضافا  
السواء  
التي ذاب

Volume  
Distribution

**With charcoal in beaker:**



Dose = 10 mg  
 $C_p^0 = 2 \text{ mg/L}$   
Apparent  
Volume = 5000 ml

ليس حجم  
الوعاء الحقيقي

انما

Cont,

The more the drug penetrate into tissues/organs following the administration of the dose, the smaller will be the plasma and/or serum drug concentration → →

Therefore the higher is the hypothetical volume into which the drug is distributed

- **$V_D$  is usually a property of a drug rather than of a biological system:** the extent to which certain drug is distributed in the body tissues

Cont,



- Reflects the extend of drug distribution in the body tissues and organs

↑ drug distribution → ↑  $V_D$

e.g.

- Highly protein bound or highly water soluble drugs

→ ↓ distribution → ↓  $V_D$

- Drugs accumulated in adipose tissues → ↑  $V_D$

- Reflects the lipophilicity of a drug

↑ drug lipophilicity → ↑  $V_D$

↑ drug hydrophilicity → ↓  $V_D$

# List of volume of distribution of some drugs

## Volume of Distribution

|                |         |             |
|----------------|---------|-------------|
| Erythropoietin | 5 L     | 0.07 L/kg*  |
| Warfarin       | 8 L     | 0.12 L/kg*  |
| Phenytoin      | 45 L    | 0.63 L /kg* |
| Digoxin        | 500 L   | 7 L /kg*    |
| Amiodarone     | 5000 L  | 70 L /kg*   |
| Chloroquine    | 15000 L | 215 L/kg*   |
| Quinacrine     | 35000 L | 500 L/kg*   |

\* **Distribution Coefficient**

هو constant لكل drug ولكن  $\frac{\text{per kg}}{\text{وزن الجسم}}$  بفرق حسب

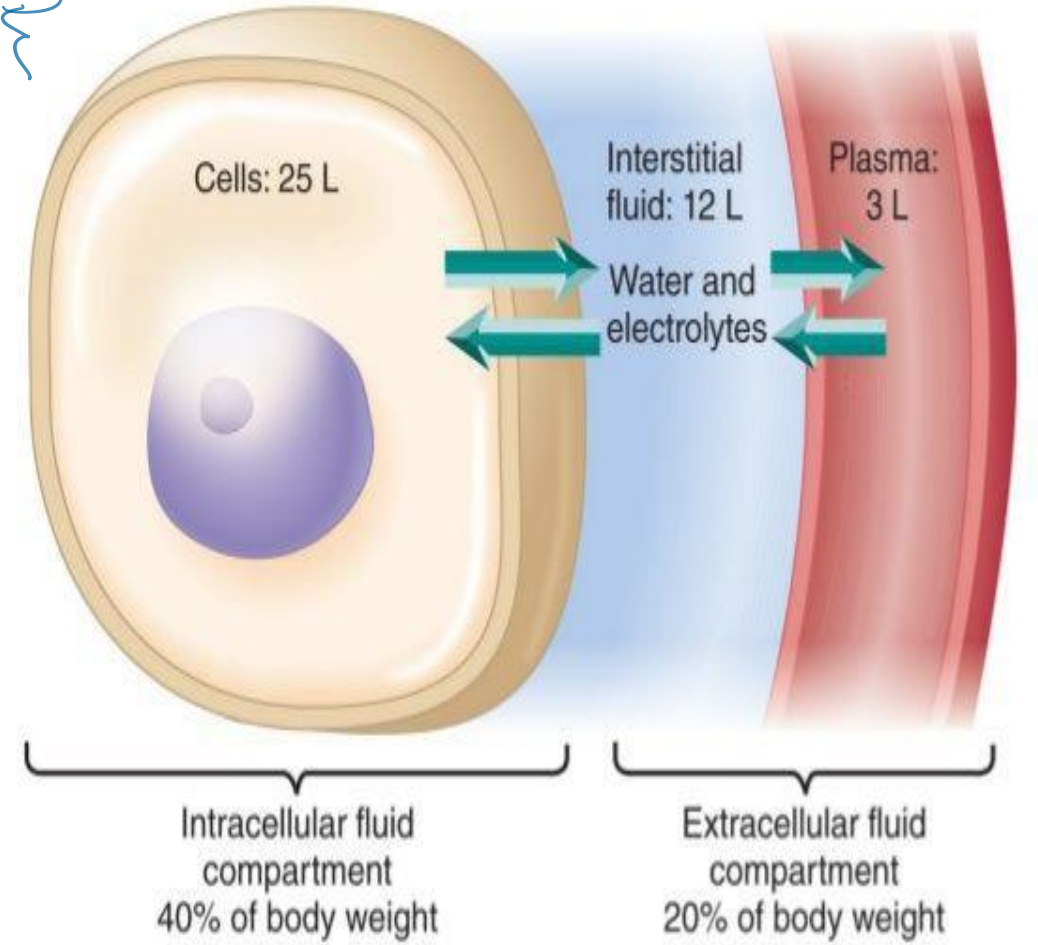
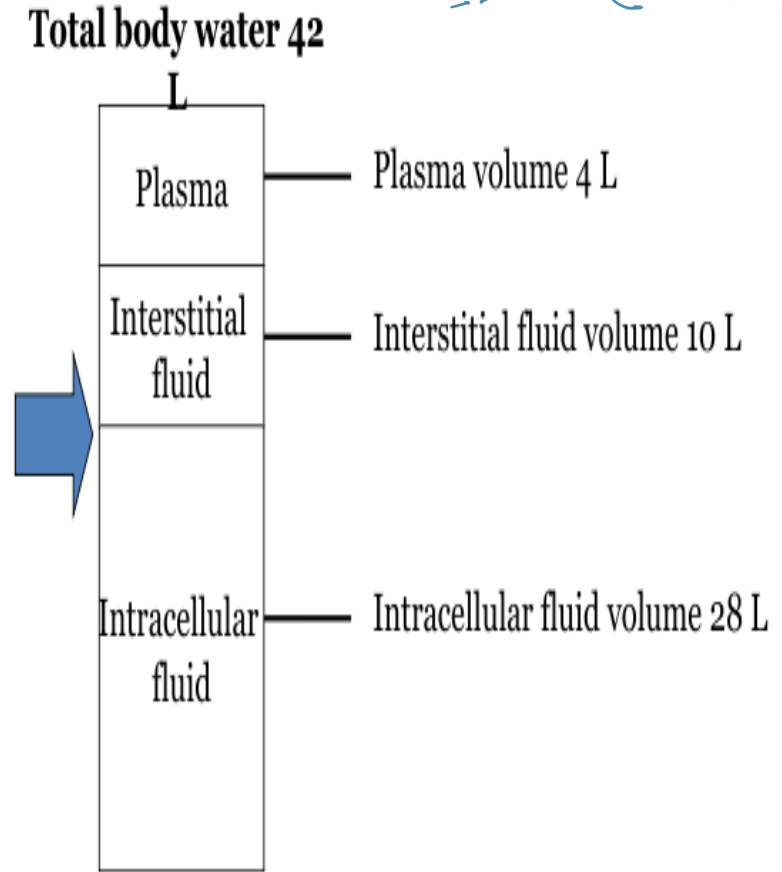
Distribution volume

إفاد ما أعطتك وزن العنصر ولا حركته per kg فهذا يكون حجم

The real Volume of Distribution has physiological meaning and is related to body water

Major fluid compartments in the body

نعم تتحرك بالسلاسل



# Apparent Volume of Distribution

- If a drug has a high molecular weight or is extensively protein bound, it is too large to pass through the slit junctions of the capillaries and, thus, is effectively trapped within the plasma (vascular) compartment. As a result, it has a low  $V_d$  that approximates the plasma volume, or **about 4 L in a 70-kg individual** (e.g. Heparin).
- If a drug has a low molecular weight but is hydrophilic, it can pass through the endothelial slit junctions of the capillaries into the interstitial fluid. However, hydrophilic drugs cannot move across the lipid membranes of cells to enter the intracellular fluid. Therefore, these drugs distribute into a volume that is the sum of the **plasma volume and the interstitial fluid**, which together constitute the extracellular fluid, (about 20% of body weight or 14 L in a 70-kg individual) ( e.g. aminoglycoside antibiotics)

# Apparent Volume of Distribution

افضل Case

tissue + binding  
de w  
+  
hydrophlicity  
خلط

- If a drug has a low molecular weight and has enough lipophilicity, it can move into the interstitium through the slit junctions and pass through the cell membranes into the intracellular fluid. These drugs distribute into a volume of about 60% of body weight or about 42 L in a 70-kg individual. *Ethanol* exhibits this apparent Vd.

بالامتعان بيهي سواد ←

- In general, a larger Vd indicates greater distribution into tissues; a smaller Vd suggests confinement to plasma or extracellular fluid.

Drug X has a volume of distribution of 20 L/kg, what does this mean?

20 \* وانه

70

الوزن الطبيعي \*

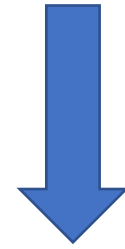
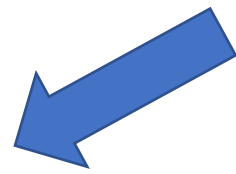
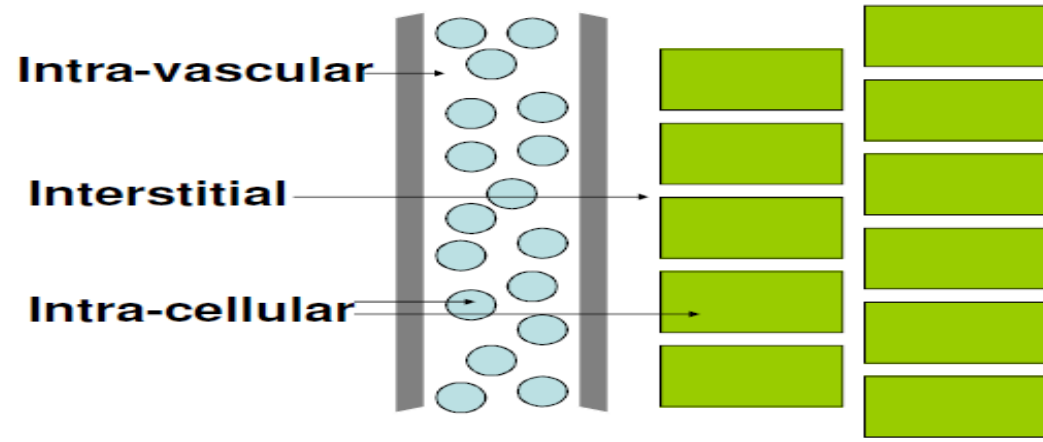
سكن ما يجبله  
اليد

# Volume of distribution

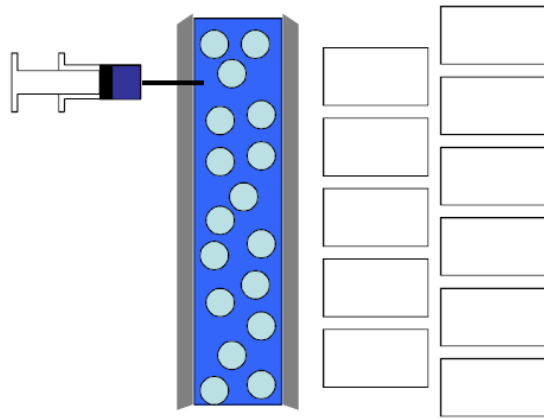
Capitolo

- The apparent volume of distribution has a minimum value that is dependent on physiological factors. A drug must be distributed at least throughout the plasma. Therefore, the minimum value of the apparent volume of distribution should be at least 3–4 L in a healthy 70 kg subject.
- There is theoretically, however, no upper limit. The higher the tissue affinity, the lower the fraction of drug will be in plasma.
- Theoretically, if the plasma concentration approaches a value of zero at infinitely high tissue affinities, the value of the volume of distribution moves towards infinity.

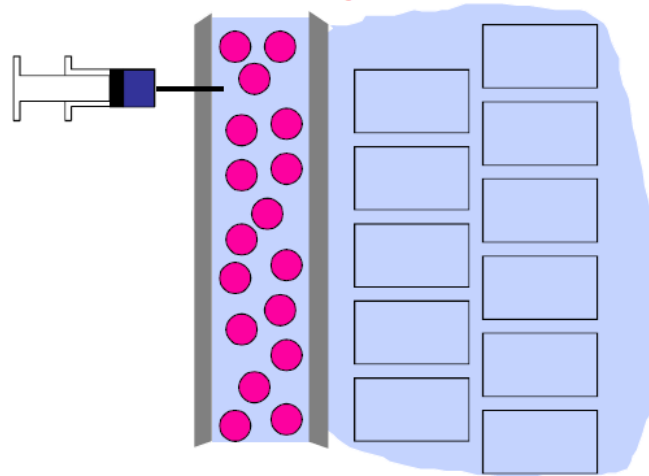
# Body water



**Distribution - Evan's Blue**  
Intra-vascular space only



**Distribution - Ethanol**  
All water



**Distribution - Quinacrine**  
Concentration into cells

