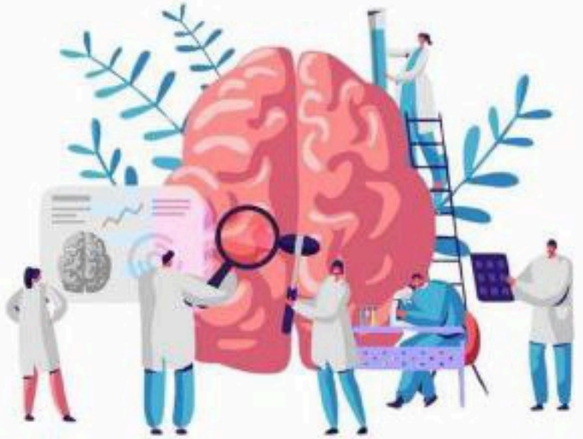


تفريغ لحاينتك

محاضرة: Non-linear pharmacokinetic

الصيدلاني\ة: Alaa Otoum

لجان الدُّفعات

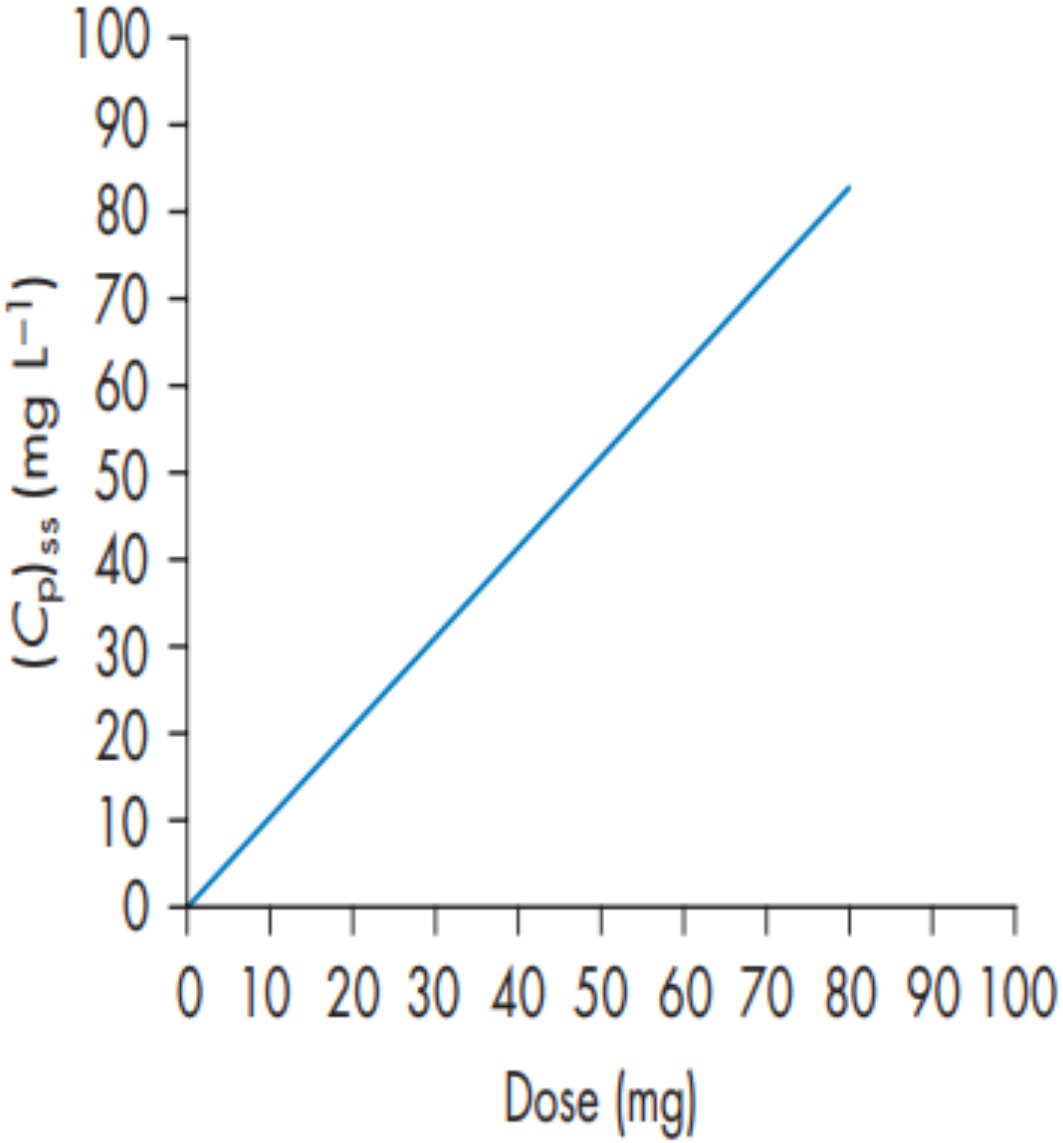
Soul Academy

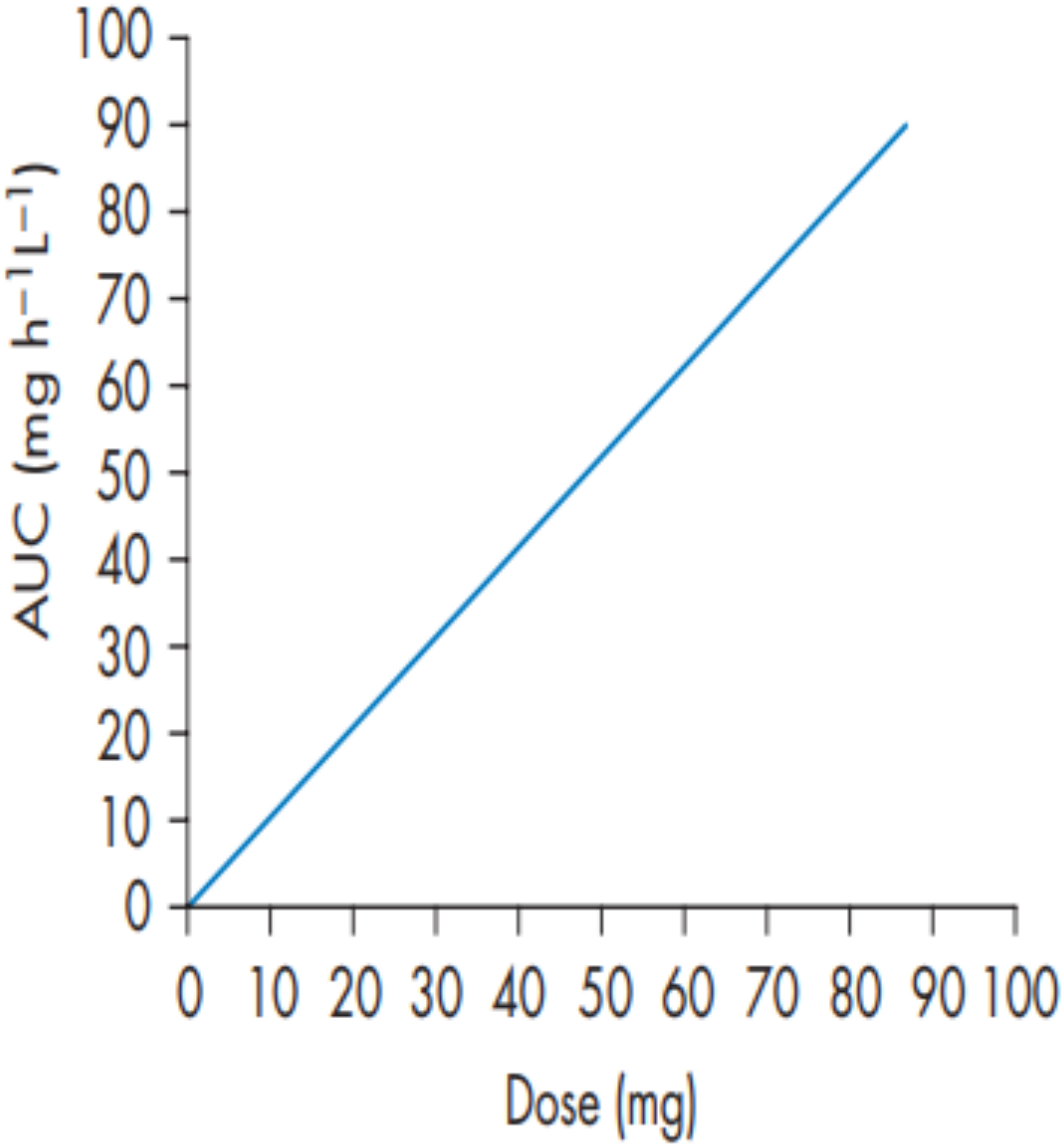
Non-linear pharmacokinetic

PK theory lec-21

Linear PK

- k, V_D, Cl and $t_{0.5}$ → Do not change when different doses are administered and/or when the drug is administered via different routes as a single or multiple doses
- Linear PK → Dose independent → First order process

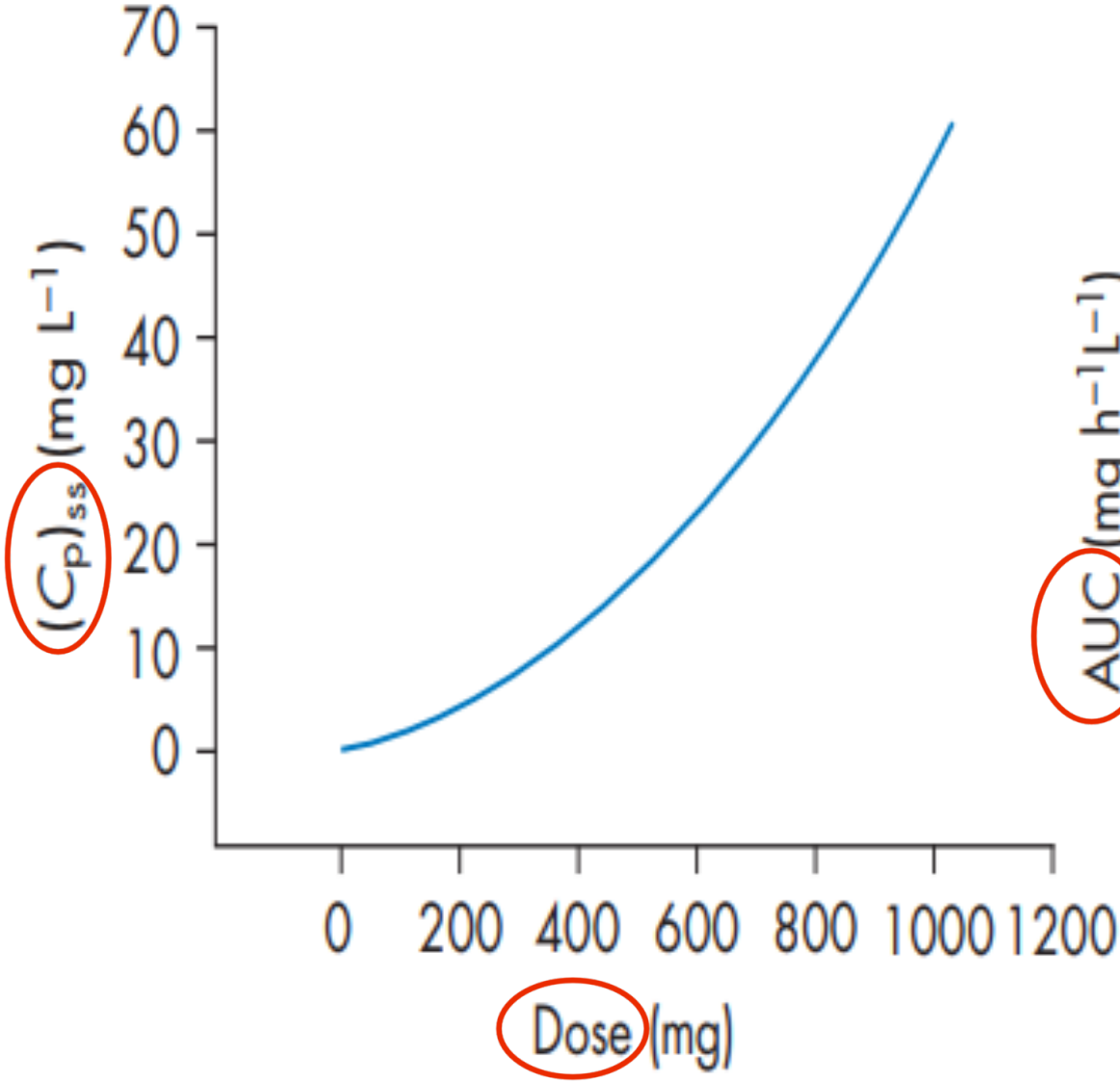

100
90
80
70
60
50
40
30
20
10
0
$(C_p)_{ss}$ (mg L^{-1})
0 10 20 30 40 50 60 70 80 90 100
Dose (mg)

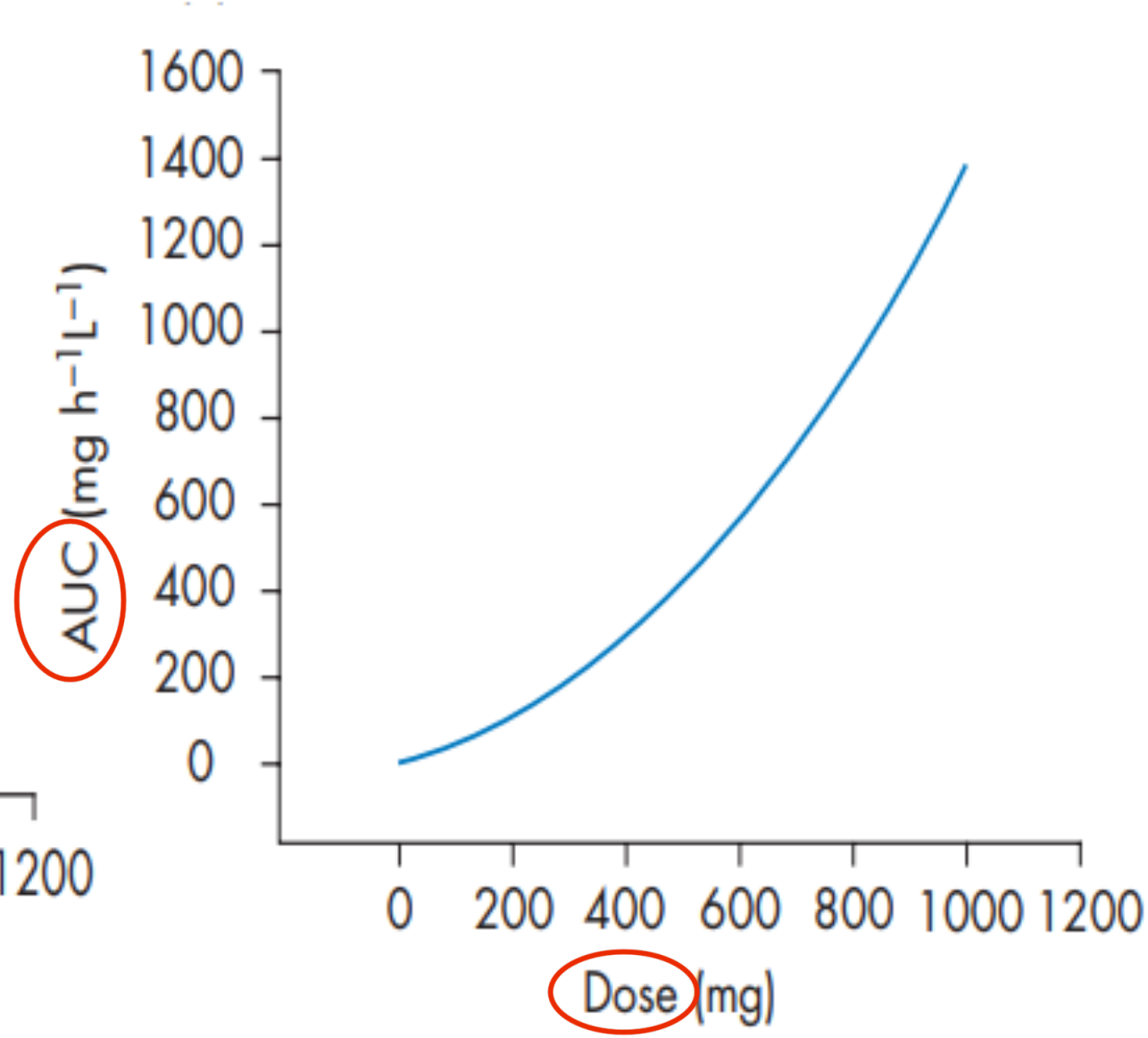

100
90
80
70
60
50
40
30
20
10
0
AUC (mg $h^{-1}L^{-1}$)
0 10 20 30 40 50 60 70 80 90 100
Dose (mg)

Nonlinear PK

تتغير بتغير الdose أو الroute of administration

- PK parameters→ change when different doses are administered and/or when the drug is administered via different routes as a single or multiple doses
- Dose dependent kinetics→ involve processes other than 1st order
- Saturation PK = Capacity-limited PK= Michaelis-Menten PK= Mixed-order PK
- Drug absorption, distribution, metabolism, and excretion


70
60
50
40
30
20
10
0
$(C_p)_{ss}$ (mg L^{-1})
0
200
400
600
800
1000
1200
Dose (mg)


1600
1400
1200
1000
800
600
400
200
0
AUC (mg $h^{-1}L^{-1}$)
0
200
400
600
800
1000
1200
Dose (mg)

Examples of Drugs Showing Nonlinear Kinetics

Cause[a]	Drug
GI Absorption	
Saturable transport in gut wall	Riboflavin, gebapentin, l-dopa, baclofen, ceftibuten
Intestinal metabolism	Salicylamide, propranolol
Drugs with low solubility in GI but relatively high dose	Chorothiazide, griseofulvin, danazol
Saturable gastric or GI decomposition	Penicillin G, omeprazole, saquinavir
Distribution	
Saturable plasma protein binding	Phenylbutazone, lidocaine, salicylic acid, ceftriaxone, diazoxide, phenytoin, warfarin, disopyramide
Cellular uptake	Methicillin (rabbit)
Tissue binding	Imiprimine (rat)
CSF transport	Benzylpenicillins
Saturable transport into or out of tissues	Methotrexate

ممنوع مطلوب

Examples of Drugs Showing Nonlinear Kinetics

Renal Elimination	
Active secretion	Mezlocillin, para-aminohippuric acid
Tubular reabsorption	Riboflavin, ascorbic acid, cephapirin
Change in urine pH	Salicylic acid, dextroamphetamine
Metabolism	
Saturable metabolism	Phenytoin, salicyclic acid, theophylline, valproic acid[b]
Cofactor or enzyme limitation	Acetaminophen, alcohol
Enzyme induction	Carbamazepine
Altered hepatic blood flow	Propranolol, verapamil
Metabolite inhibition	Diazepam
Biliary Excretion	
Biliary secretion	Iodipamide, sulfobromophthalein sodium
Enterohepatic recycling	Cimetidine, isotretinoin

[a]Hypothermia, metabolic acidosis, altered cardiovascular function, and coma are additional causes of dose and time dependencies in drug overdose.

[b]In guinea pig and probably in some younger subjects.

Data from Evans et al (1992).

Table 9-1: Applied BP and PK book

Dr. Ruba Darweesh, Spring'18-19

مش مطلوب

Nonlinear metabolism

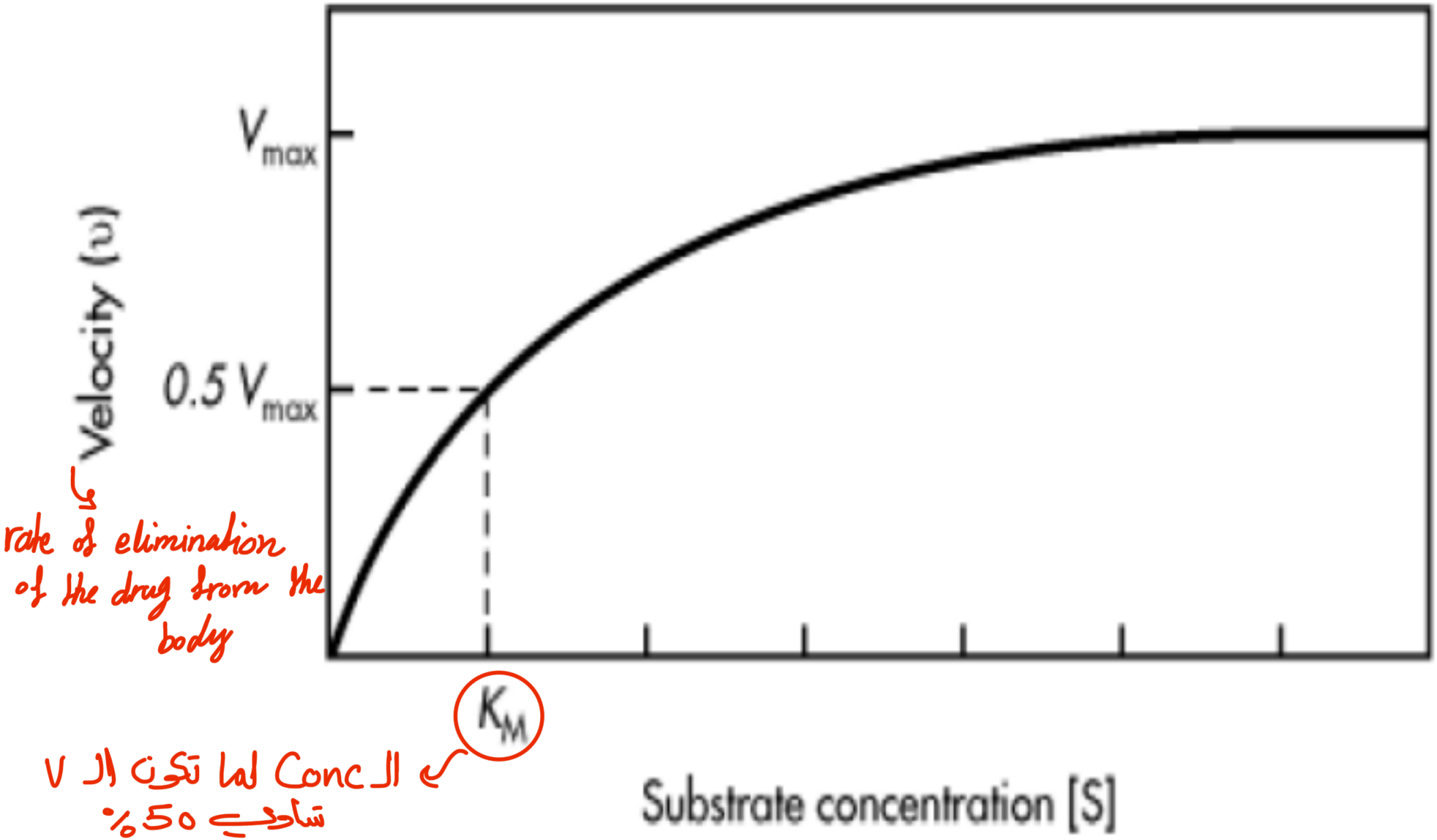
- One of the most common source of nonlinearity ??
- Enzymatic reactions:

لأنه جال metabolism ممكنا من قبل انه فيها phase I , phase II وبتعتمد على enzyme معاي
ال enzyme مع تربط بالـ substrate وبعدها بيص عندي metabolism of drug.

نظرية القفل والمفتاح -

Enzyme+ Substrate (drug) → Enzyme-drug complex → Enzyme+ Metabolite

$$[E] + [D] \leftrightarrow [ED] \rightarrow [M] + [E]$$



rate of elimination of the drug from the body

الـ Conc لما تكون الـ V تساوي ٥٠٪

Enzyme kinetics: MM eqt.

$$v = \frac{V_{max} \times [D]}{[D] + K_M}$$

Units:
V_{max}: mass/time
K_m: mass/volume
C=[D]: concentration unit (mass/vol)

conc of 50% of Vmax

- **v**: velocity or rate of the reaction = the rate for the formation of the product (metabolite) or the rate of elimination of the drug
- **V_{max}:** The maximum velocity→ the theoretical maximum rate of the elimination process
- **C or [D]:** total drug concentration
- **K_m:** drug concentration when the velocity (**v**) of the reaction is equal to one-half the maximum velocity → **C @ 0.5 V_{max}**

50%

MM-eqt.: At low drug concentration

- $[D] << K_M$

$$v = \frac{V_{max} \times [D]}{[D] + K_M}$$

$$v = \frac{V_{max} \times [D]}{K_M}$$

هاي المعادلة تمثل First order بما انه في عندي fraction ثابت بس كمية ثابتة ف الـfraction بمثل ثابت واذا بضربه بال dose بضل عندي مقدار التناقص بتغير بناءً على الـconstant يعني هو proportional لـ amount الموجودة عندي وبالتالي تمثل first order

- Both V_{max} and K_M are constants

$$v = Constant \times [D]$$

- This represents ??

MM-eqt.: At high drug concentration

- [D] >> K_M

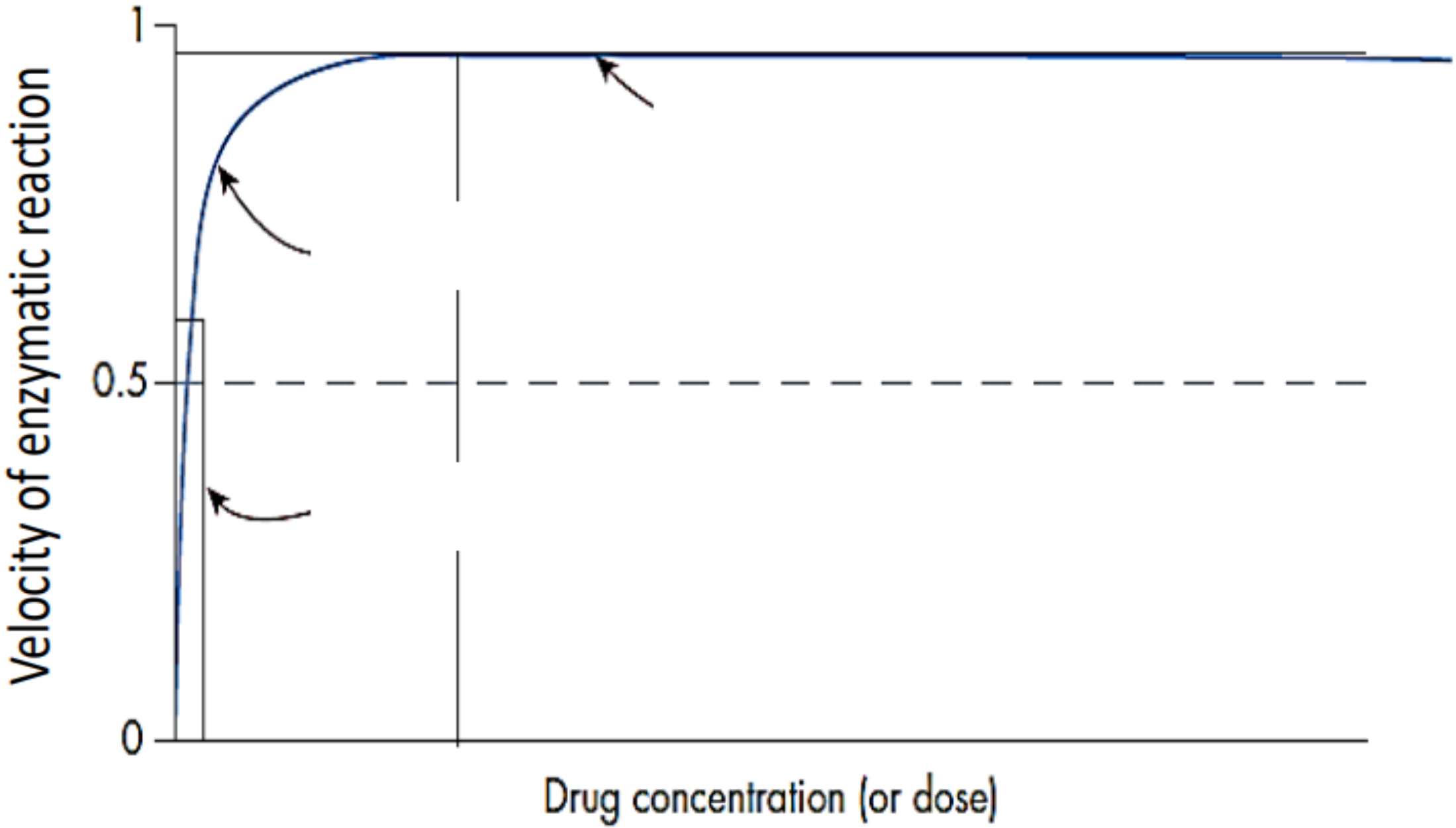
$$v = \frac{V_{max} \times [D]}{[D] + K_M}$$

$$v = \frac{V_{max} \times [D]}{[D]}$$

$$v = V_{max}$$

Zero order

- This represents ??


1
0.5
0
Velocity of enzymatic reaction
Drug concentration (or dose)

Cp vs. time profile after single IV-Bolus

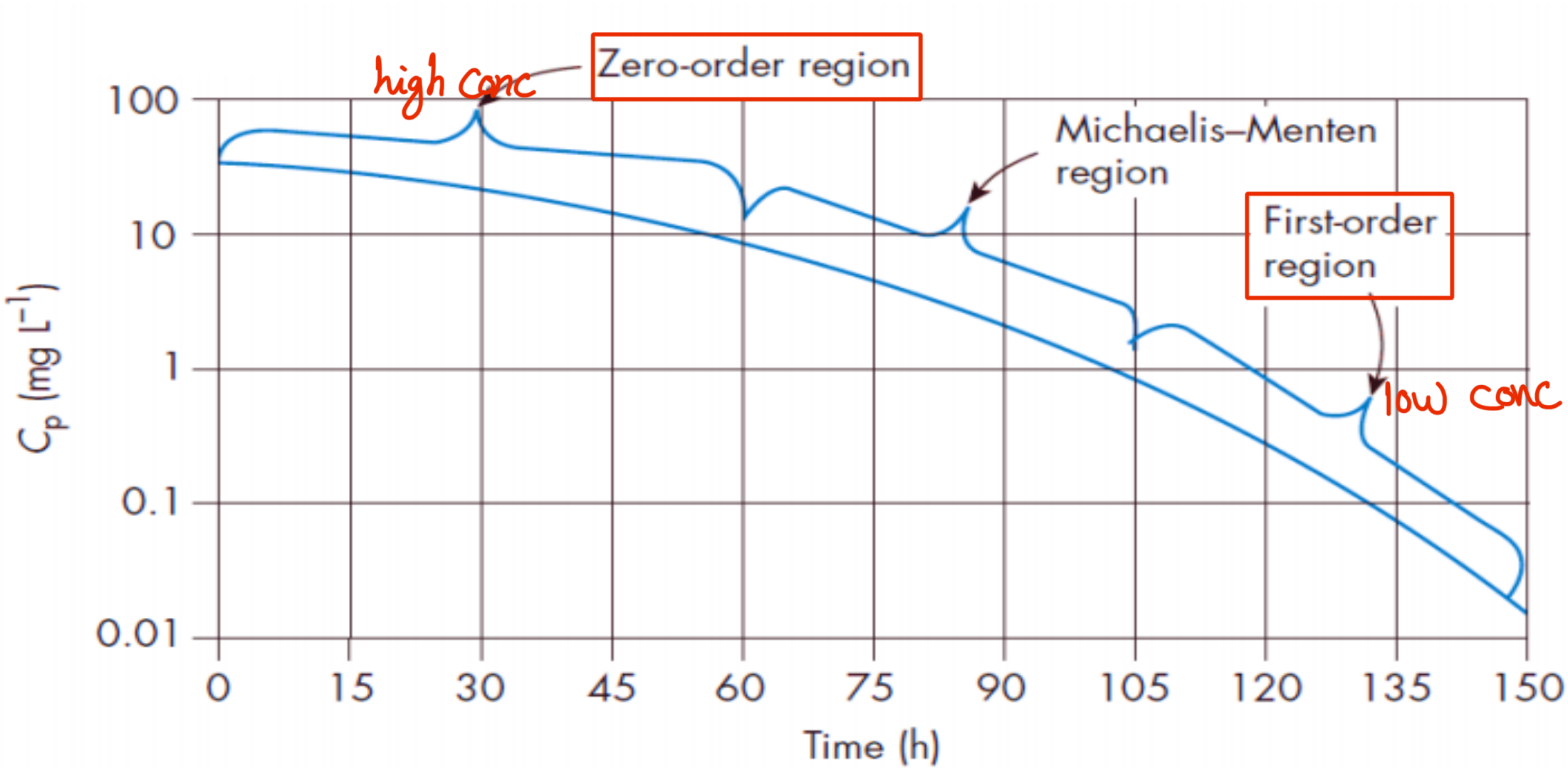


TABLE 2-4. First-Order Elimination

Time after Drug Administration (hours)	Amount of Drug in Body (mg)	Amount of Drug Eliminated over Preceding Hour (mg)	Fraction of Drug Eliminated over Preceding Hour
0	1000	—	—
1	880	120	0.12
2	774	106	0.12
3	681	93	0.12
4	599	82	0.12
5	527	72	0.12
6	464	63	0.12
7	408	56	0.12

بتغير

ثابت

Click to add text

The amount of drug eliminated **may change with the amount of drug in the body**
The fraction (or percentage) of a drug in the body **eliminated over a given time remains constant**

TABLE 2-5. Zero-Order Elimination

Time after Drug Administration (hours)	Amount of Drug in Body (mg)	Amount of Drug Eliminated over Preceding Hour (mg)	Fraction of Drug Eliminated over Preceding Hour
0	1000	—	—
1	850	150	0.15
2	700	150	0.18
3	550	150	0.21
4	400	150	0.27
5	250	150	0.38

ثابت

متغير

The amount of drug eliminated does **not change** with the amount or concentration of drug in the body
The fraction (or percentage) of a drug in the body **eliminated over a given time is changing**

Estimation of MM-parameters

V_{max} and K_m

1. Estimation of Michaelis–Menten parameters from administration of **a single dose**
2. Estimation of Michaelis–Menten parameters following administration **of multiple doses**

Estimation of MM-parameters from administration of **a single dose**

- The reciprocal of the Michaelis–Menten equation

بنقلب المعادلة

$$\frac{1}{v} = \frac{K_M}{V_{max}} \times \frac{1}{[D]} + \frac{1}{V_{max}}$$

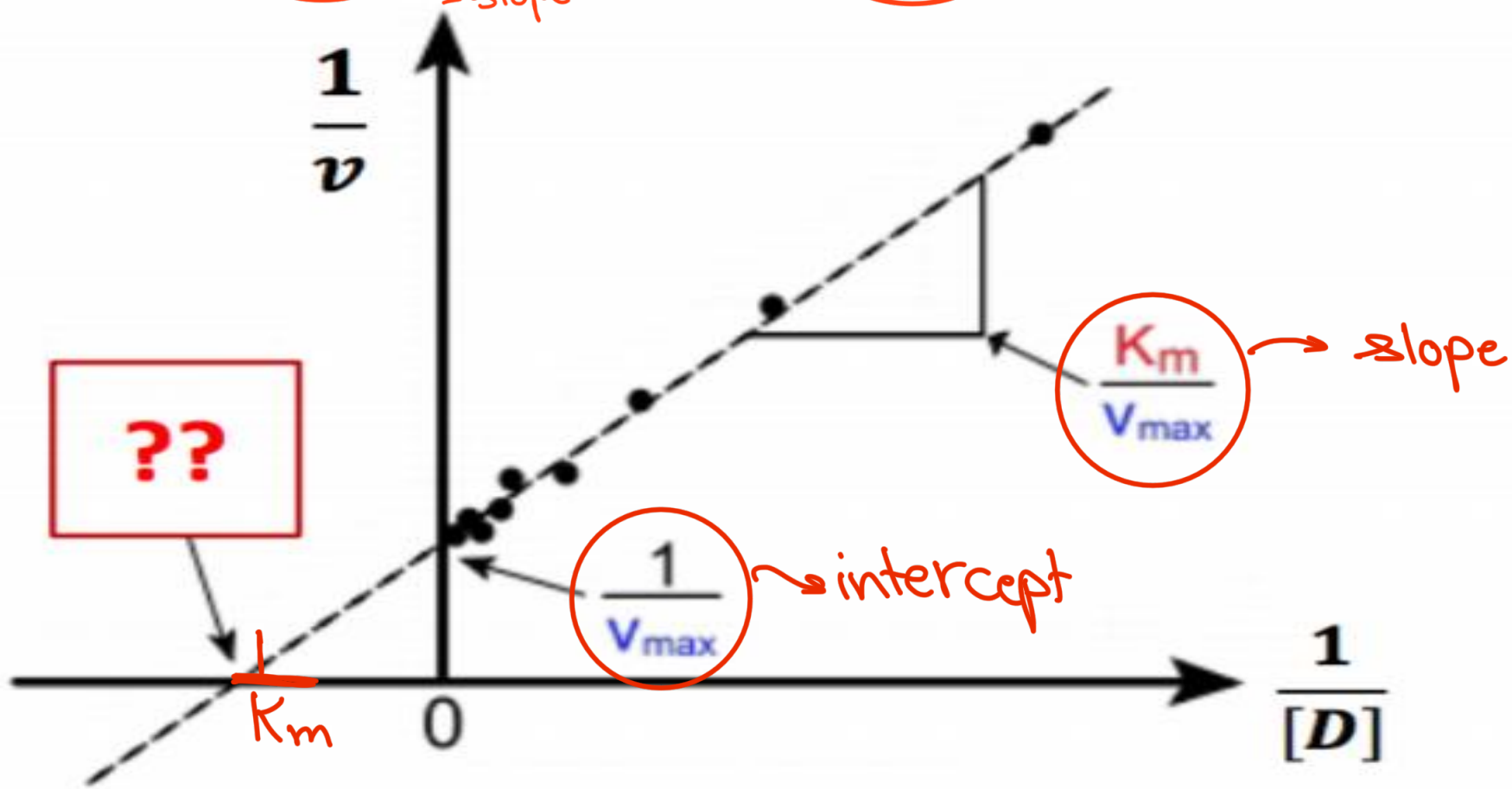
- Lineweaver–Burk plot? ⟶

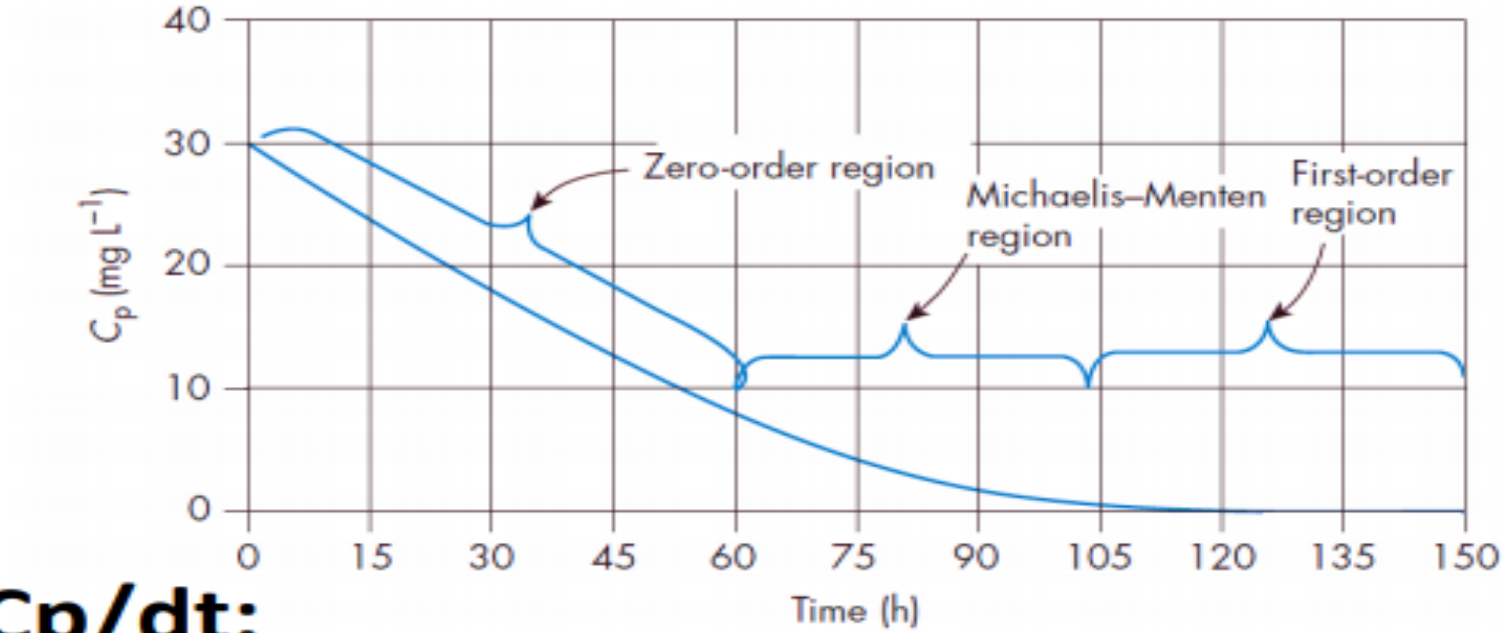
Lineweaver–Burk equation:

$$\frac{1}{v} = \frac{K_M}{V_{max}} \times \frac{1}{[D]} + \frac{1}{V_{max}}$$

slope

intercept





Practically:

1. Determine dCp/dt:

(rate: mass/vol. time)

$$dCp/dt = \Delta Cp/\Delta t$$

$$= Cp_2 - Cp_1/(t_2 - t_1)$$

2. Take the average concentration = midpoint conc.

(mass/vol.)

$$(Cp)_t = (Cp_0 + Cp_1)/2$$

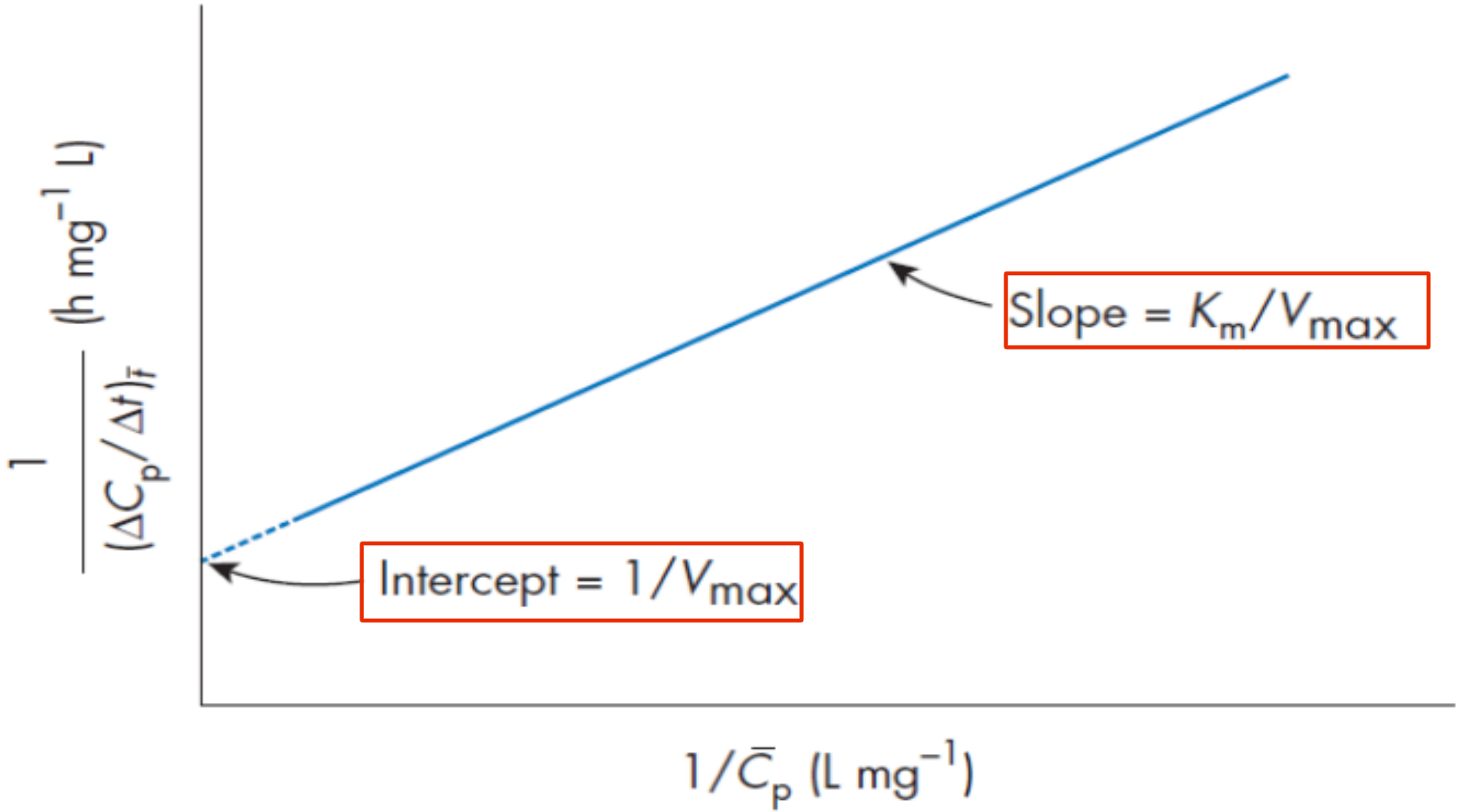
- MM-eqt. (Practical expression)

$$\left(\frac{\Delta C_{\mathrm{P}}}{\Delta t}\right)_{\bar{t}} = \frac{V_{\max}(\overline{C}_{\mathrm{P}})_{\bar{t}}}{K_{\mathrm{m}} + (\overline{C}_{\mathrm{P}})_{\bar{t}}}$$

↳ avg

- Lineweaver–Burk equation of it:

$$\frac{1}{\left(\frac{\Delta C_{\mathrm{P}}}{\Delta t}\right)_{\bar{t}}} = \left(\frac{K_{\mathrm{m}}}{V_{\max}} \cdot \frac{1}{(\overline{C}_{\mathrm{P}})_{\bar{t}}}\right) + \frac{1}{V_{\max}}$$


$\frac{1}{(\Delta C_p/\Delta t)_{\bar{r}}}$ (h mg^{-1} L)
Slope = K_m/V_{max}
Intercept = $1/V_{max}$
$1/\bar{C}_p$ (L mg^{-1})

Estimation of MM-parameters

After multiple doses at steady state

- The rate of metabolism (or elimination) at steady state will be a function of the steady-state plasma concentration → $(Cp)_{ss}$
- So, elimination or metabolism rate =

$$v = \frac{V_{max} \times Cp_{ss}}{Cp_{ss} + K_m}$$

- At ss, the **drug elimination rate** is assumed to **be equal to dosing rate (R) = Drug input (R)** → **e.g. dose/day**

Rate in = Rate out

- Then, $$R = \frac{V_{max} \times Cp_{ss}}{Cp_{ss} + K_m}$$

  R: Rate of drug input

- Many methods are used for MM- parameters estimation, one of them is:

$$R[K_m + (C_p)_{ss}] = V_{max}(C_p)_{ss}$$

$$RK_m + R(C_p)_{ss} = V_{max}(C_p)_{ss}$$

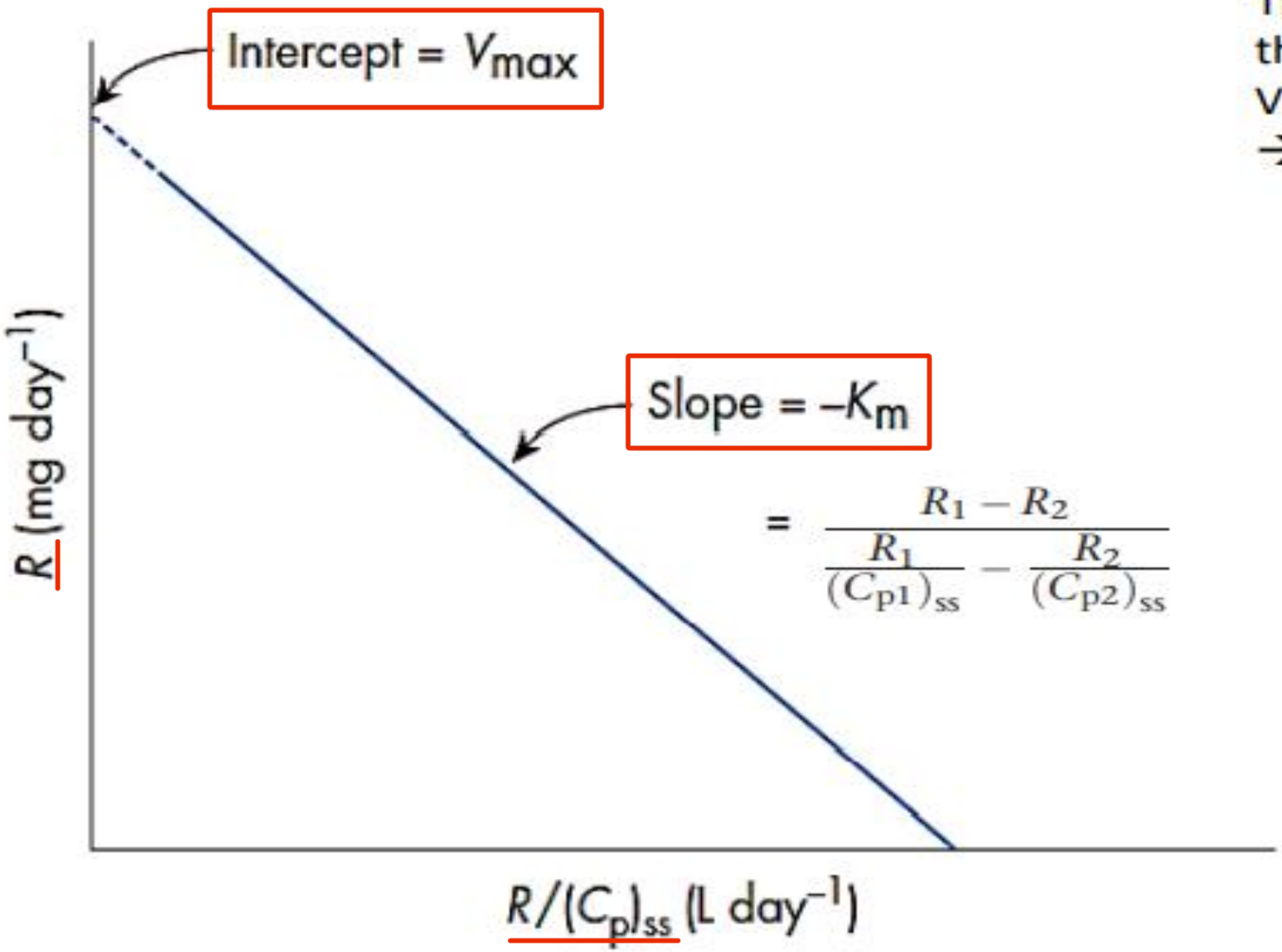
$$R(C_p)_{ss} = V_{max}(C_p)_{ss} - RK_m$$

$$R = [V_{max}(C_p)_{ss} - RK_m]/(C_p)_{ss}$$

$$R = V_{max} - [K_m \times R/(C_p)_{ss}]$$

V_{max}: intercept

K_m: slope



This profile and the estimation of the values of MM parameters (i.e. V_{max} and K_m)

→ at **least two doses (three or four is ideal)** with their corresponding **steady state plasma** concentration values

Then after Km is determined; you can determine Vmax by using the following eqt:

$$R = \frac{V_{max}(C_p)_{ss}}{K_m + (C_p)_{ss}}$$

Example 1:

Phenytoin has an estimated values of Km and Vmax of 6.5 mg/L and 548 mg/day, respectively.

It is desired to obtain a steady-state plasma concentration of 15 mg/L, what is the dosing rate of phenytoin needed to obtain such concentration?

$$R = \frac{V_{max} * C_{ss}}{K_m + C_{ss}} = \frac{548 * 15}{6.5 + 15}$$

Example 2:

Phenytoin has an estimated values of Km and Vmax of 6.5 mg/L and 548 mg/day, respectively. What would be the steady-state plasma concentrations of doses of 100, 200, 300, 400, and 450 mg per day.

Css ?

$$\text{Daily drug dose} = -K_m \left(\frac{\text{Daily dose}}{C_{ss}}\right) + V_{max}$$

or

$$C_{ss} = \frac{K_m \times \text{Daily dose}}{V_{max} - \text{Daily dose}}$$

e.g.: $C_{ss} = \frac{6.5 * 100}{548 - 100}$

Nonlinear PK:

- **Nonlinear PK means that there is a non-proportionality between AUC and dose**
  - X/AUC ratio is not constant
  - Cl =X/AUC is not constant
  - Elimination rate constant k=CL/V is not constant (assuming that V is constant)
  - There is no true $t_{0.5}$ (not constant)
- Time to reach the ss is not constant, and can't be predicted
- Therefore → time (**in days**) to reach 90% of the ss ($t_{90\%ss}$) is usually estimated by:

$$= \frac{K_m V}{(V_{max} - R)^2}(2.303 V_{max} - 0.9R) = t_{0.9}$$

Example 3:

If a drug has V_{max} of 500 mg/day, V (apparent volume of distribution) of 50 L, Km of 4 ug/mL. Determine the time required to reach 90% of the ss concentration for the following daily 100, 200, 300, 400 mg doses.

جالأول نحسب R من القانون تبع

$$R = \frac{V_{max} * C_{ss}}{K_m + C_{ss}}$$

Sol: $R = \frac{500 * 100}{4 + 100} = 480.77$

بعد هيك بدل على هاد القانون

$$= \frac{K_m V}{(V_{max} - R)^2}(2.303 V_{max} - 0.9R) = t_{0.9}$$

$$t_{0.9} = \frac{4 * 50}{(500 - 480.77)^2}(2.303 * 500 - 0.9 * 480.77)$$

$$t_{0.9} = 0.54 * 718.807$$

$$t_{0.9} = 388.15 \text{ hr}$$

Example 4:

A patient achieved a steady-state concentration (trough) of 9 mg/L after receiving 300 mg of phenytoin per day; when the daily dose was increased to 400 mg/day, a steady-state concentration of 16 mg/L was achieved.

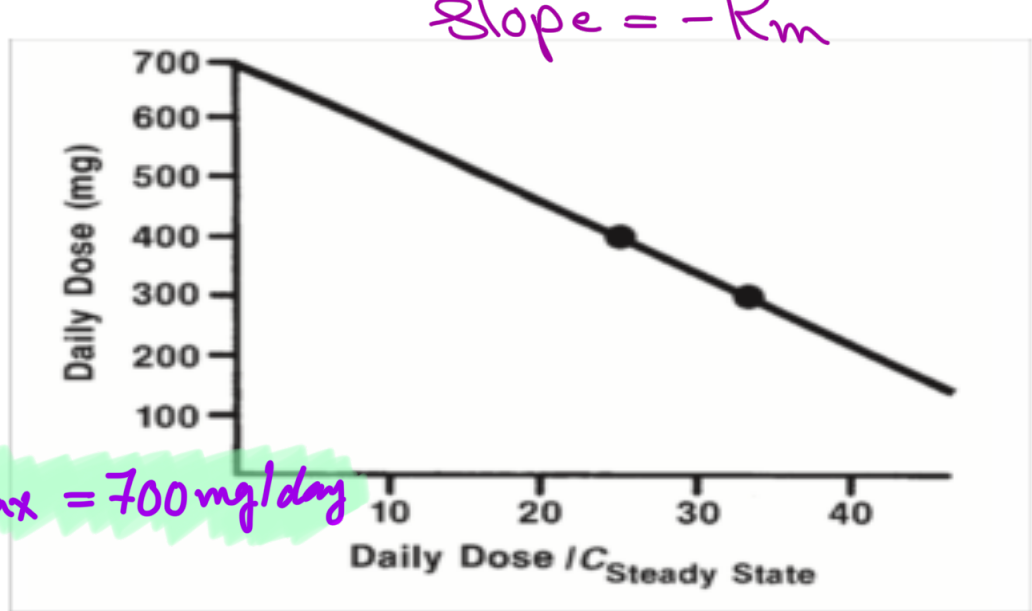
→ Determine k_m, V_{max}

$$\text{Slope} = -Km = \frac{R_1 - R_2}{\frac{R_1}{C_{ss_1}} - \frac{R_2}{C_{ss_2}}}$$

$$= \frac{300 - 400}{\frac{300}{9} - \frac{400}{16}} = 12 \text{ mg/L} = Km$$

$$R = \frac{Vmax * Css}{Km + Css}$$

e.g. $$300 = \frac{Vmax * 9}{12 + 9} \rightarrow Vmax = 700 \text{ mg/day}$$



From the graph: 12 mg/L and 700 mg per day

Example 4: Cont'd

- If you were asked to increase the steady-state plasma concentration to 20 mg/L, what would be the necessary daily dose to achieve such concentration?

$$\textbf{Daily drug dose} = \frac{V_{max} \times C_{ss}}{K_m + C_{ss}}$$

700 20 17 20

Using MM eqt: 437.5 mg per day