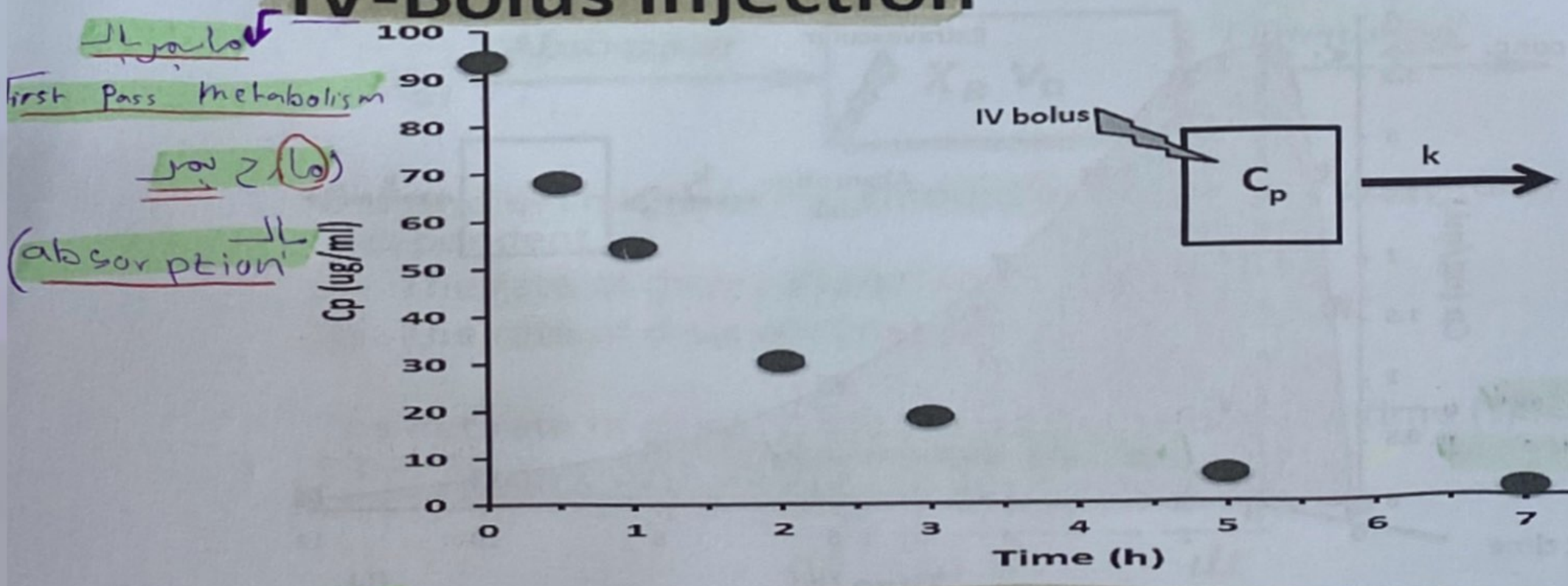
Oral administration part II

PK theory lec 10

Remember

IV-Bolus injection



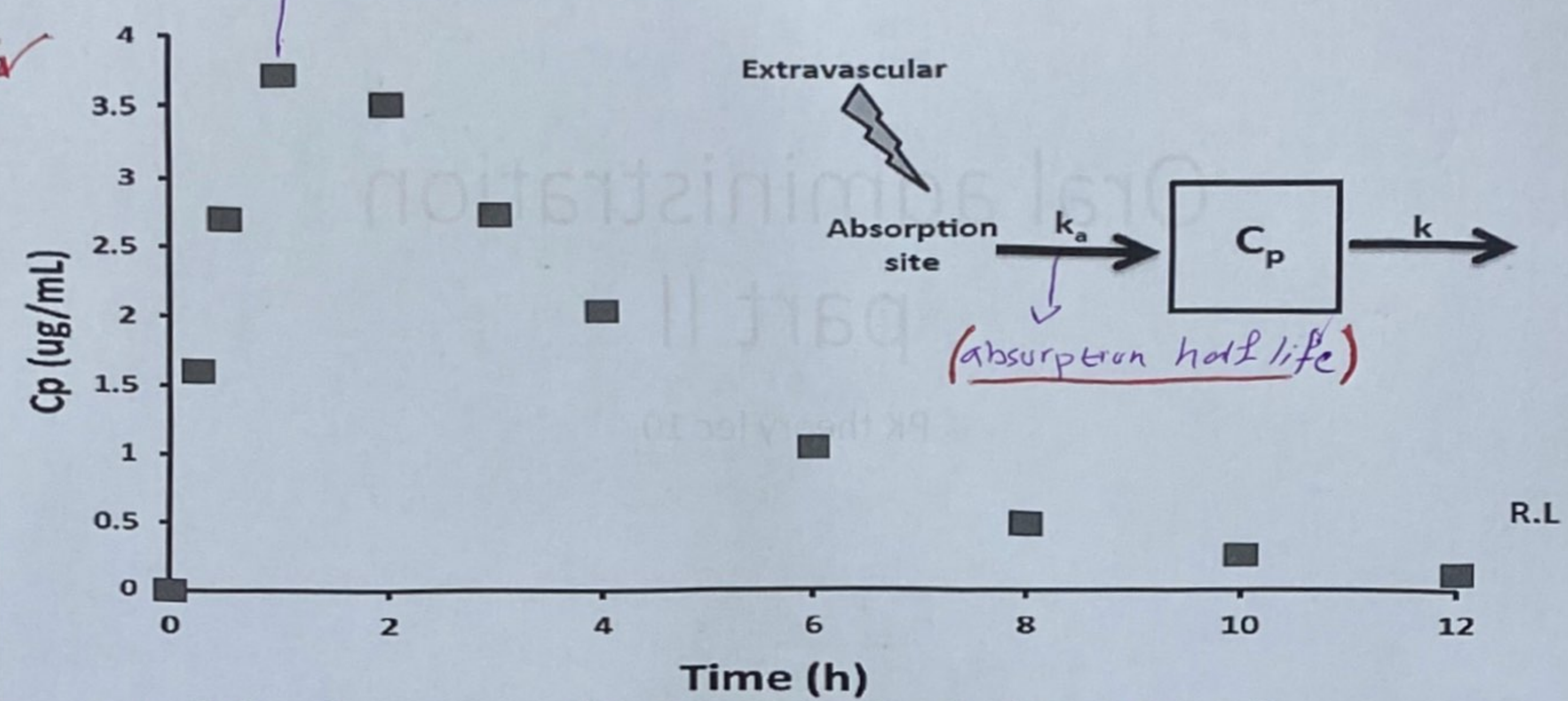
100% of the administered dose directly in the systemic circulation (t=0), followed by distribution, metabolism and elimination

absorption. فش

* Note بال oral حتى لو أوصل أعلى (Conc) مش حتكون 100% .. (يعني مش زي IV bolus, بال IV كل الدواء رح يوصل systemic circulation)

Extravascular administration

بمر بال absorption



Amount of the drug= 0, in the systemic circulation, at t=0→

Followed by absorption then distribution, metabolism and elimination

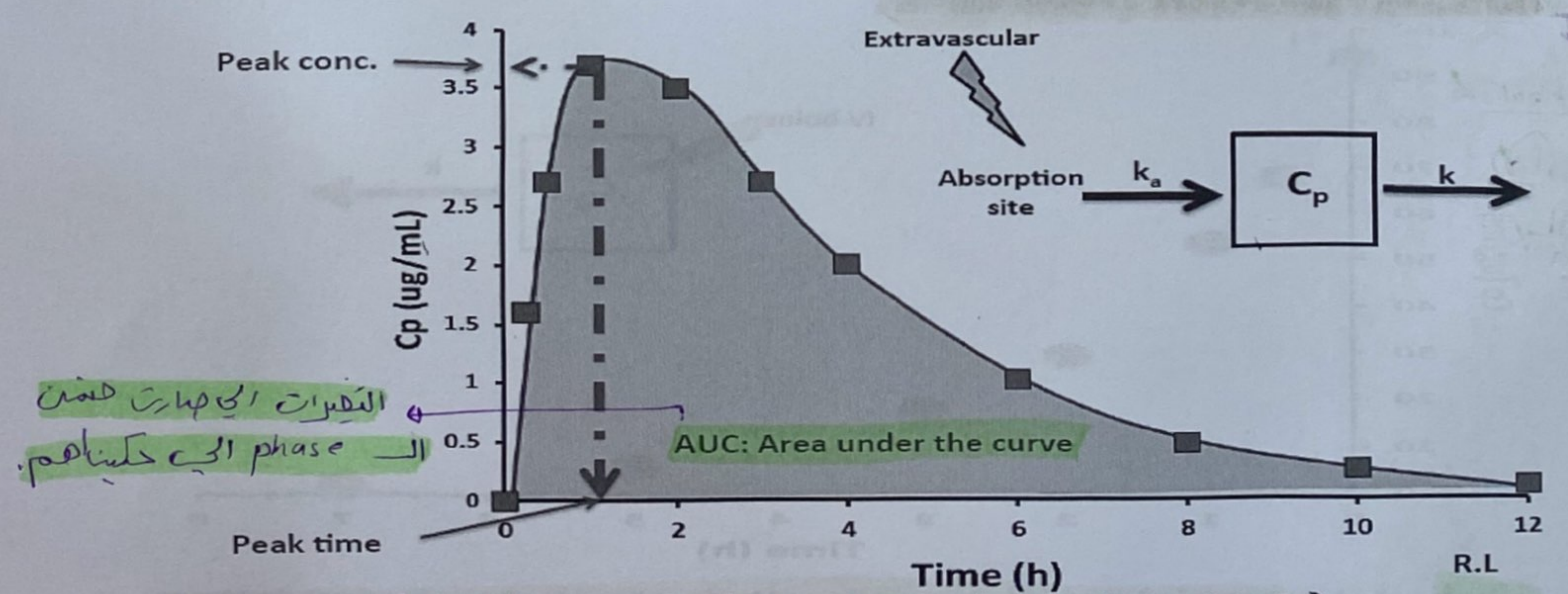
* الدواء بس أعطي ع شكل orall حكينا ال model الي رح نمشي عليه هو فقط one compartment بعد absorption phase واحد

(يعني رح يمر بال absorption phase ← one post absorption phase ← elimination phase) - بناءً ع اعتبار هون انه الدواء بكون ال distribution عالي فبنستثني الأدوية الي بتكون extended release drug.

* فهون حنأخذ ال immediate release drug

*

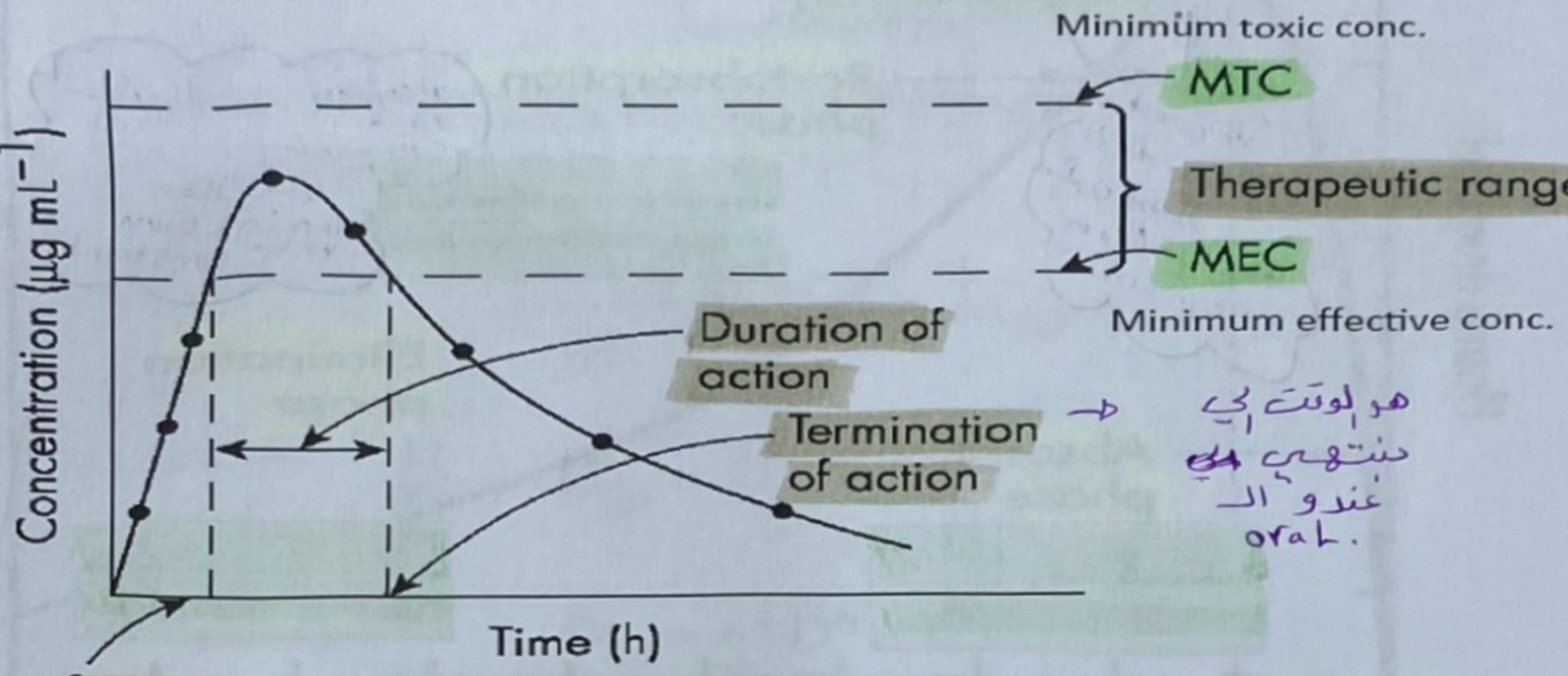
Extravascular administration



Amount of the drug= 0, in the systemic circulation, at t=0→

Followed by absorption then distribution, metabolism and elimination

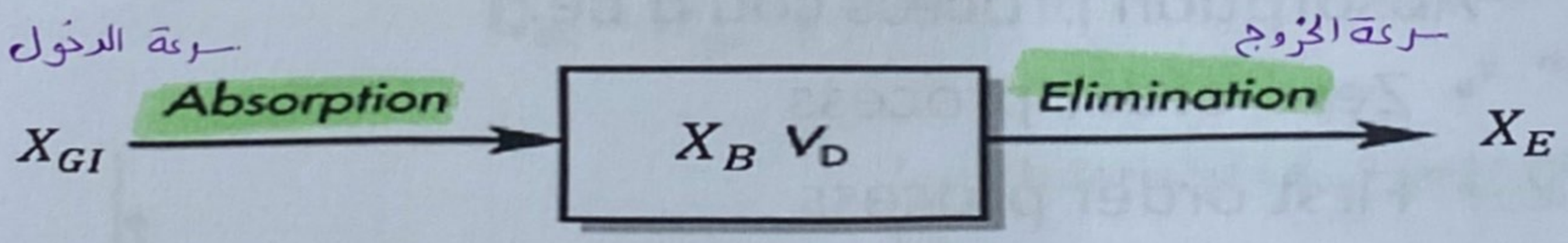
Plasma Level–Time Curve



Generalized plasma level–time curve after oral administration of a drug

First order!

Oral-One Compartment PK Model



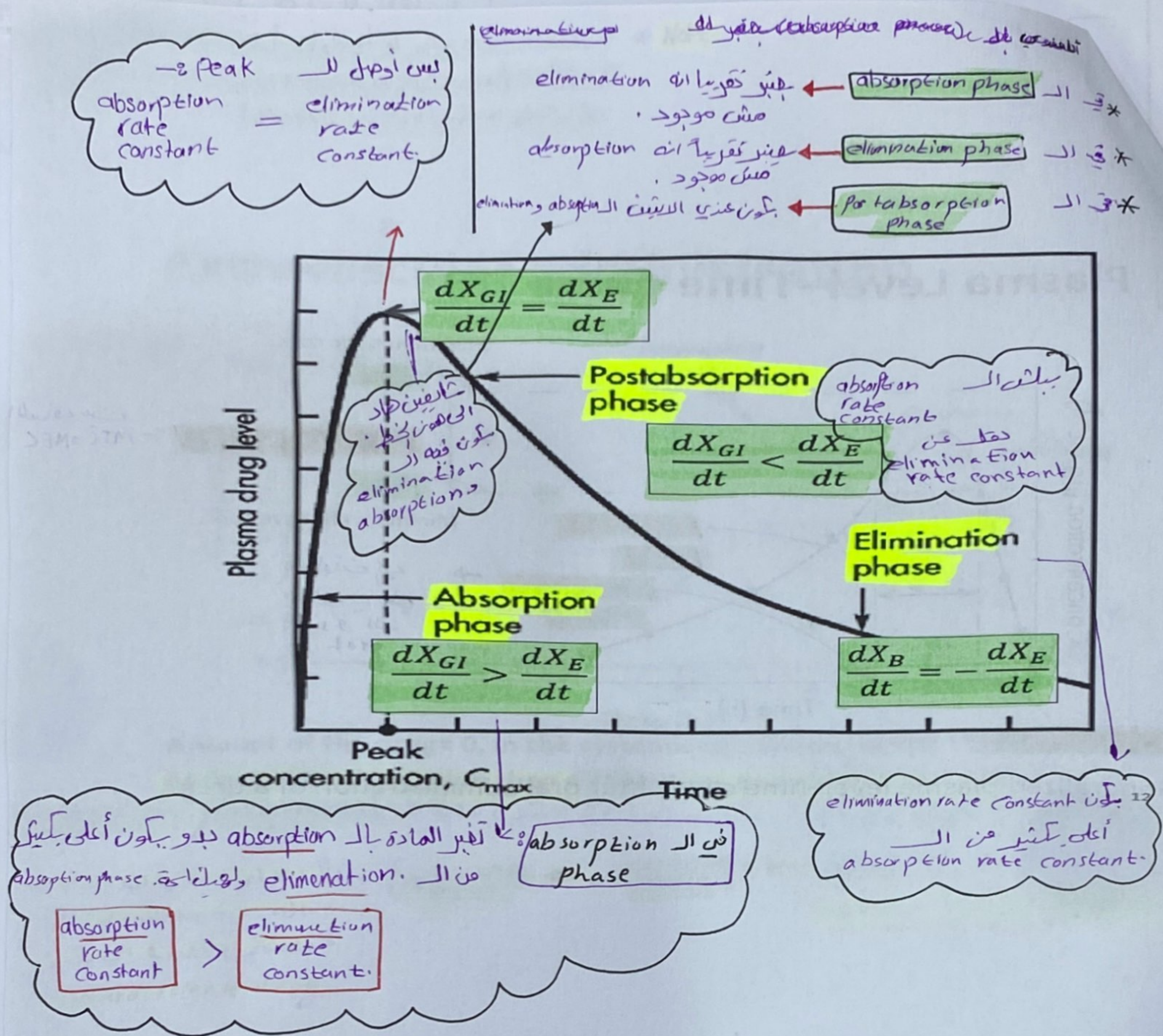
The rate of change in the amount of drug in the body (dX_B/dt) is dependent on:

1. The rate of drug absorption
2. The rate of drug elimination

The net rate of drug accumulation in the body at time (t) is equal to:

$$\frac{dX_B}{dt} = \frac{dX_{GI}}{dt} - \frac{dX_E}{dt}$$

regardless of whether absorption is zero-order or first-order.

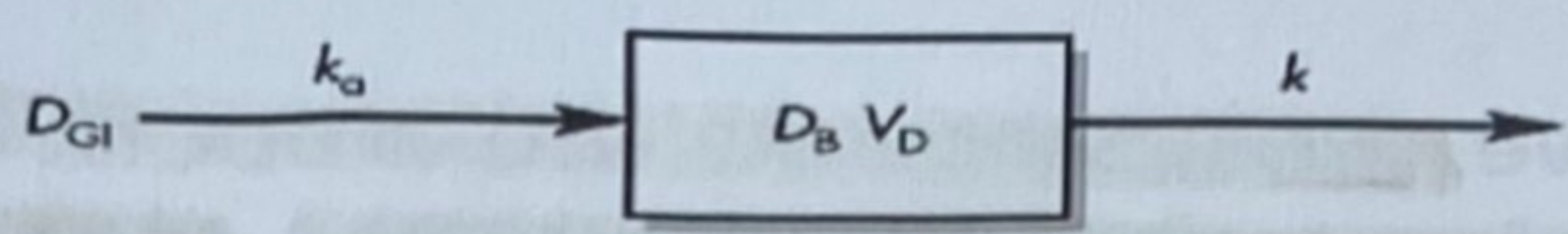


Absorption process could be:

- Zero-order process
- First order process

First-order absorption model

- Absorption is usually assumed to be a first-order process
- This model applies mostly to the oral absorption of drugs in solution or rapidly dissolving dosage forms (immediate release)



The rate of disappearance of drug from the gastrointestinal tract:

absorption rate constant

$$\frac{dD_{GI}}{dt} = -Ka \times D_{GI}$$

ال dose الي انا اعطيتها عن طريق ال GI

* مش كل ال dose الي رح توصل رح يصير عليها (absorption) ف أنا هون مجبورة اضربه بالنسبة الي حصلتها

(bioavailability) → F

$$D_{GI} = D_{GI}^0\, e^{(-ka*t)}$$

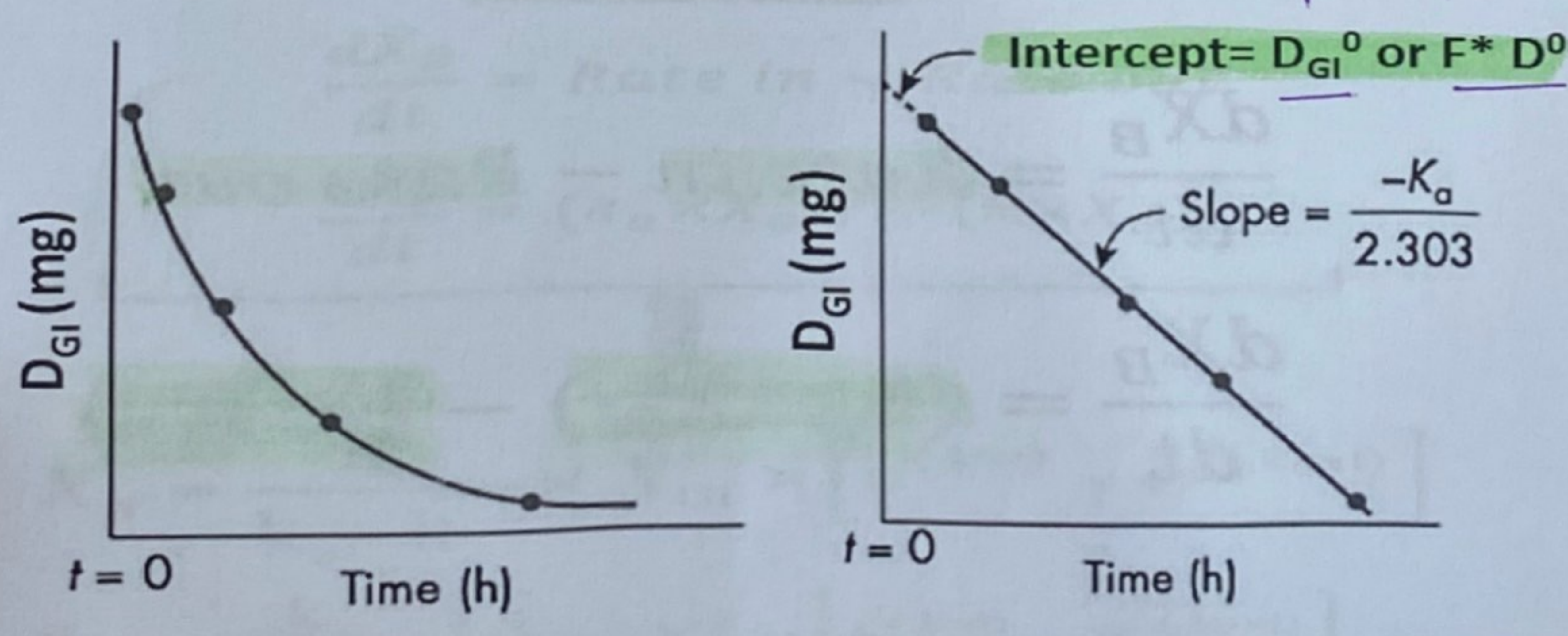
$$D_{GI} = F * D^0\, e^{(-ka*t)}$$

or $D_{GI} = D^0\, e^{(-ka*t)}$ → When?

$$D_{GI} = D_{GI}^0\, e^{(-ka*t)}$$

اذا بضرب الجرعة الاصلية (D^0) ب كم النسبة الي وصلت لل General Circulation بكون عرفت كم الجرعة الي راحت من GI

الجرعة الي بال GI



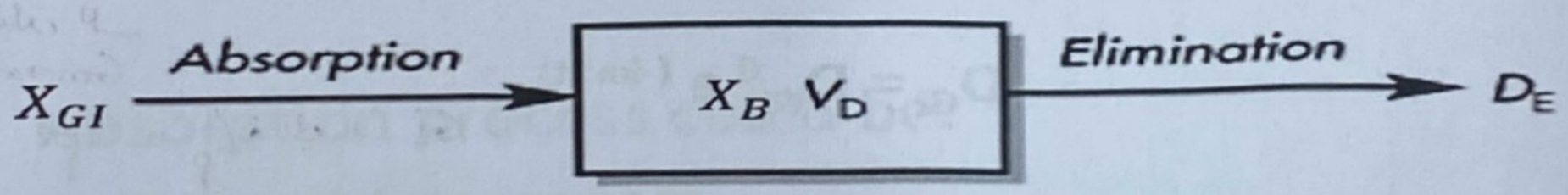
R.L S.L

Amount of drug remaining at the site of administration vs. time

- BUT, we can't measure the amount of drug remaining to be absorbed (D_{GI}) directly, because of practical difficulty

- So, previous eqt. is not useful for determining the absorption rate constant

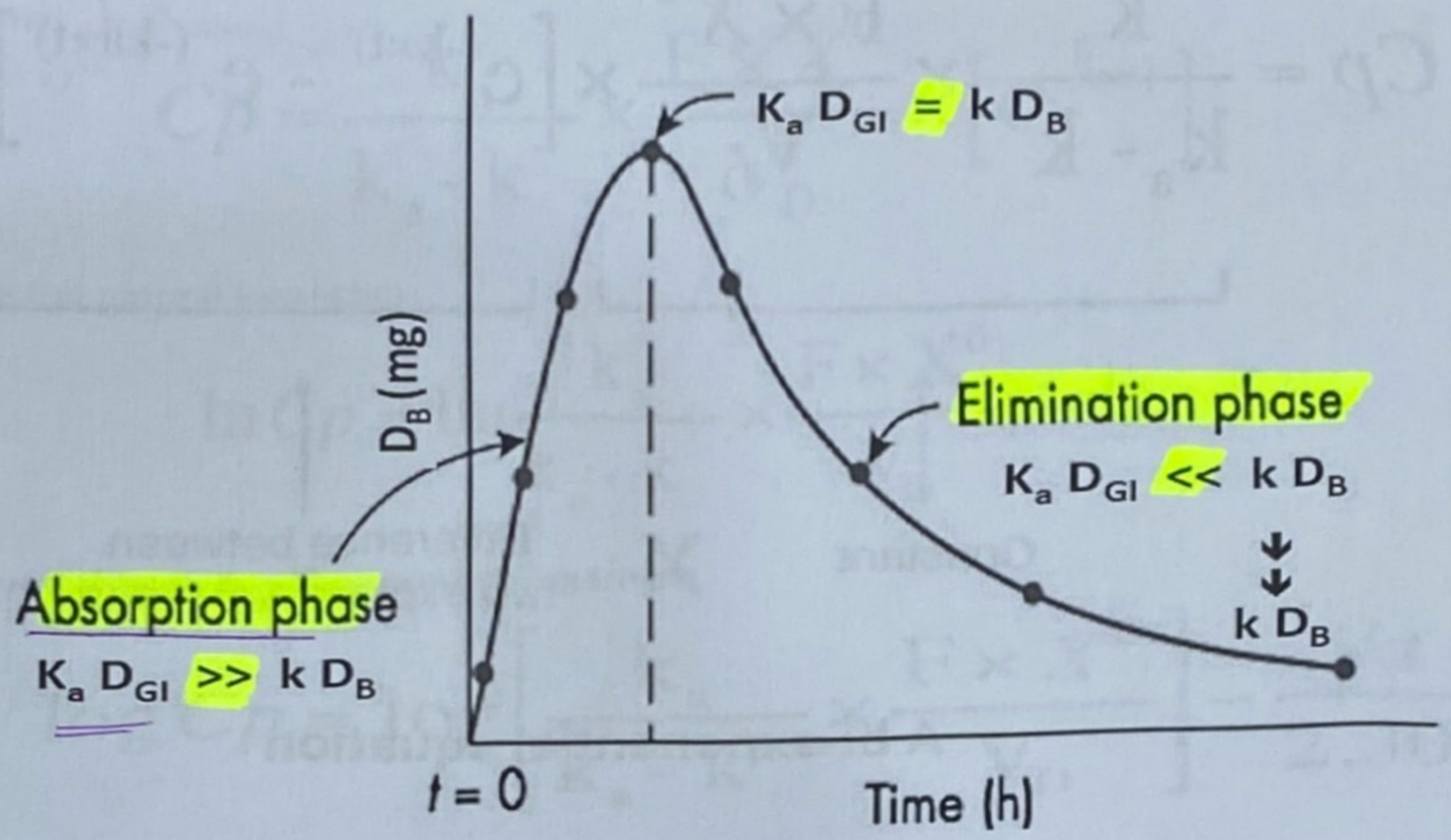
- Therefore, measurement of the drug conc. and/or mass in the blood and/or urine; is usually used to determine the absorption rate constant and the absorption characteristics

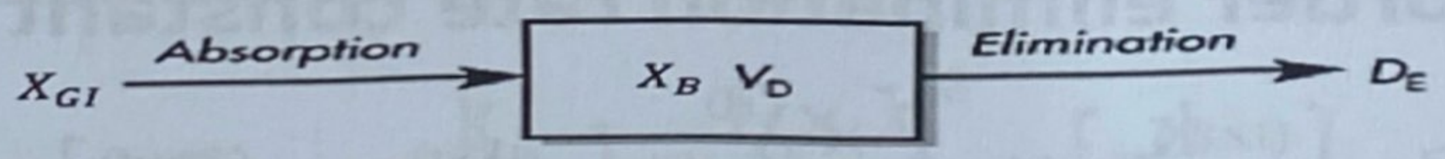


$$\frac{dX_B}{dt} = Rate\ in - Rate\ out$$

$$\frac{dX_B}{dt} = (k_a \times X_{GI}) - (k \times X_B)$$

dX_B/dt: rate (mass/time) of change of amount of the drug in the blood/plasma/serum





$$\frac{dX_B}{dt} = Rate\ in - Rate\ out$$

$$\frac{dX_B}{dt} = (k_a \times X_{GI}) - (k \times X_B)$$

نكامل لنطلع المعادلة

$$X_B = \frac{k_a}{k_a - k} \times X_{GI}^0 \times \left[e^{(-k \times t)} - e^{(-ka \times t)}\right]$$

$$X_B = \frac{k_a}{k_a - k} \times F \times X^0 \times \left[e^{(-k \times t)} - e^{(-ka \times t)}\right]$$

$$Cp = \frac{k_a}{k_a - k} \times \frac{F \times X^0}{V_D} \times \left[e^{(-k \times t)} - e^{(-ka \times t)} \right]$$

Constant X Difference between two exponential terms

A bi-exponential equation

First-order elimination rate constant (k)

$$Cp = \frac{k_a}{k_a - k} \times \frac{F \times X^0}{V_D} \times \left[e^{(-k \times t)} - e^{(-ka \times t)} \right]$$

- "k" may be determined from the elimination phase of the concentration–time profile
- At later time intervals, the drug absorption has been completed→ i.e., $e^{(-ka*t)} \approx 0$

$$Cp = \frac{k_a}{k_a - k} \times \frac{F \times X^0}{V_D} \times \left[e^{(-k \times t)} - e^{(-ka \times t)} \right] \quad (e^{(-ka \times t)} \approx 0)$$

elimination phase خلال ال
(absorption) مكينا ما يكون في

First-order elimination rate constant (k)

نحط هاي داخل القوس بس نحل.

$$Cp = \frac{k_a}{k_a - k} \times \frac{F \times X^0}{V_D} \times \left[e^{(-k \times t)}\right]$$

Take the natural logarithm

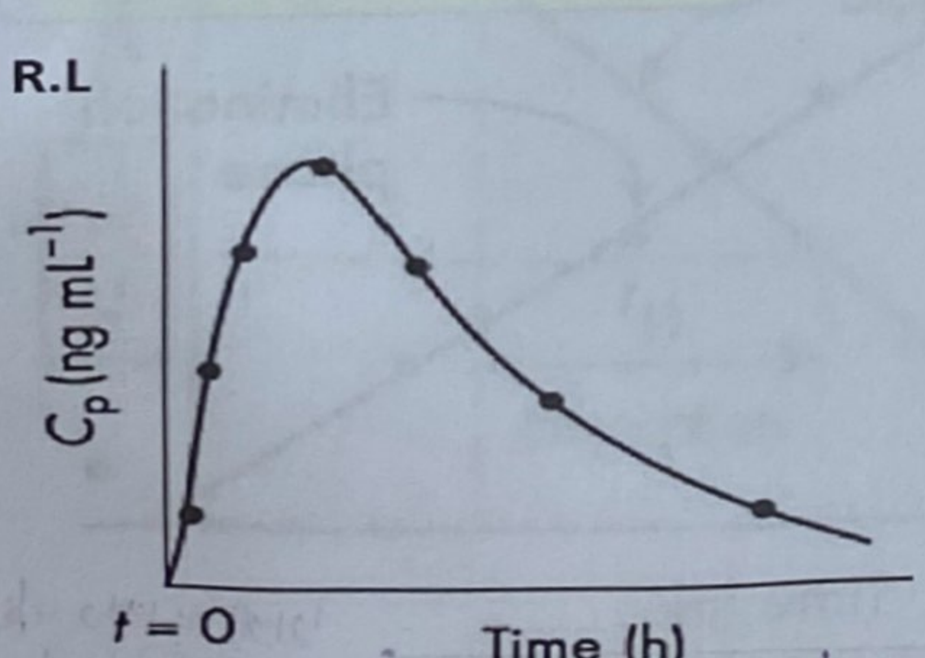
$$\ln Cp = \ln\left(\frac{k_a}{k_a - k} \times \frac{F \times X^0}{V_D}\right) - kt$$

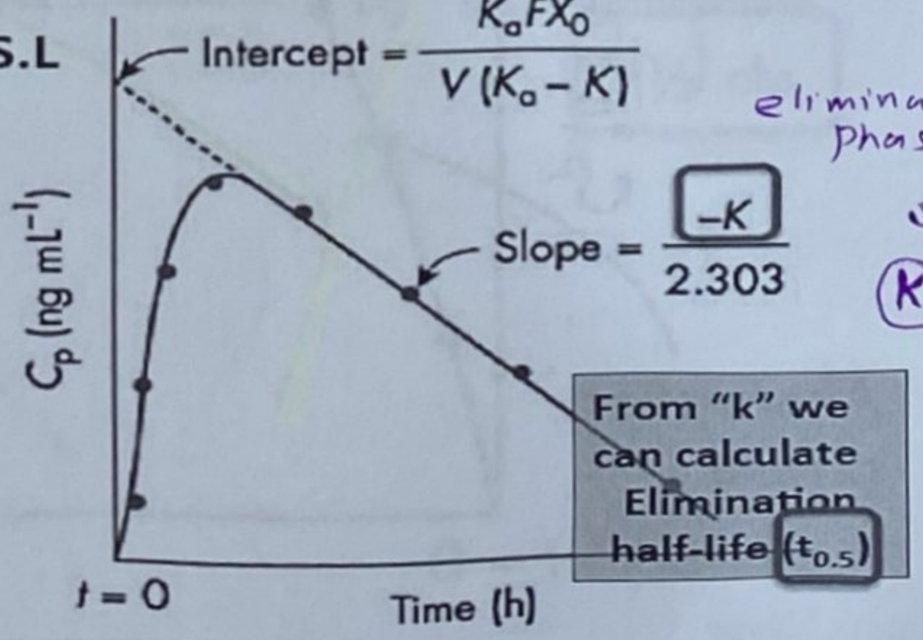
If you change it to the common logarithm

$$\log Cp = \log\left[\frac{k_a}{k_a - k} \times \frac{F \times X^0}{V_D}\right] - \frac{kt}{2.303}$$

Plasma concentration (C_p) vs. time profile

$$Cp = \frac{k_a}{k_a - k} \times \frac{F \times X^0}{V_D} \times \left[e^{(-k \times t)}\right]$$



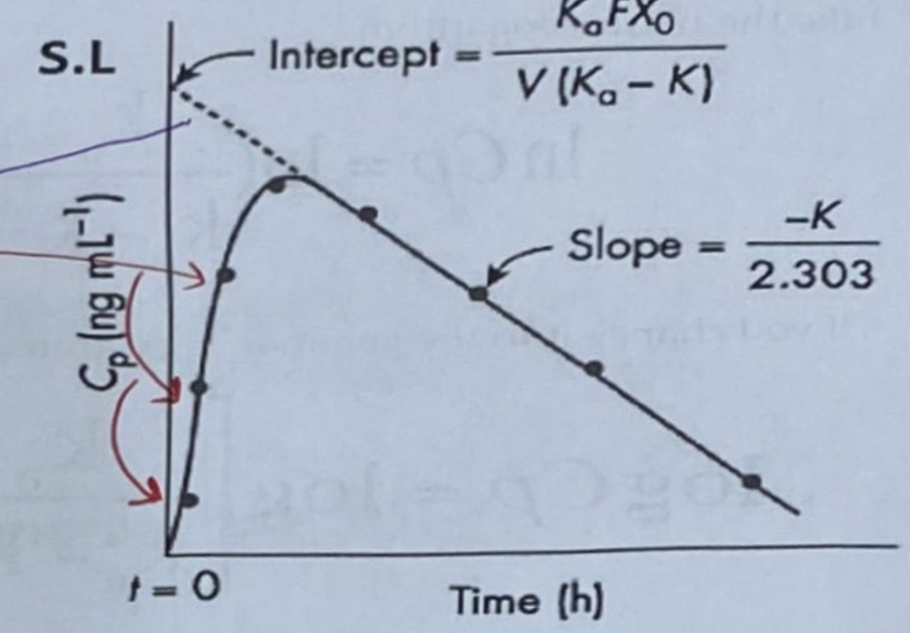


elimination phase

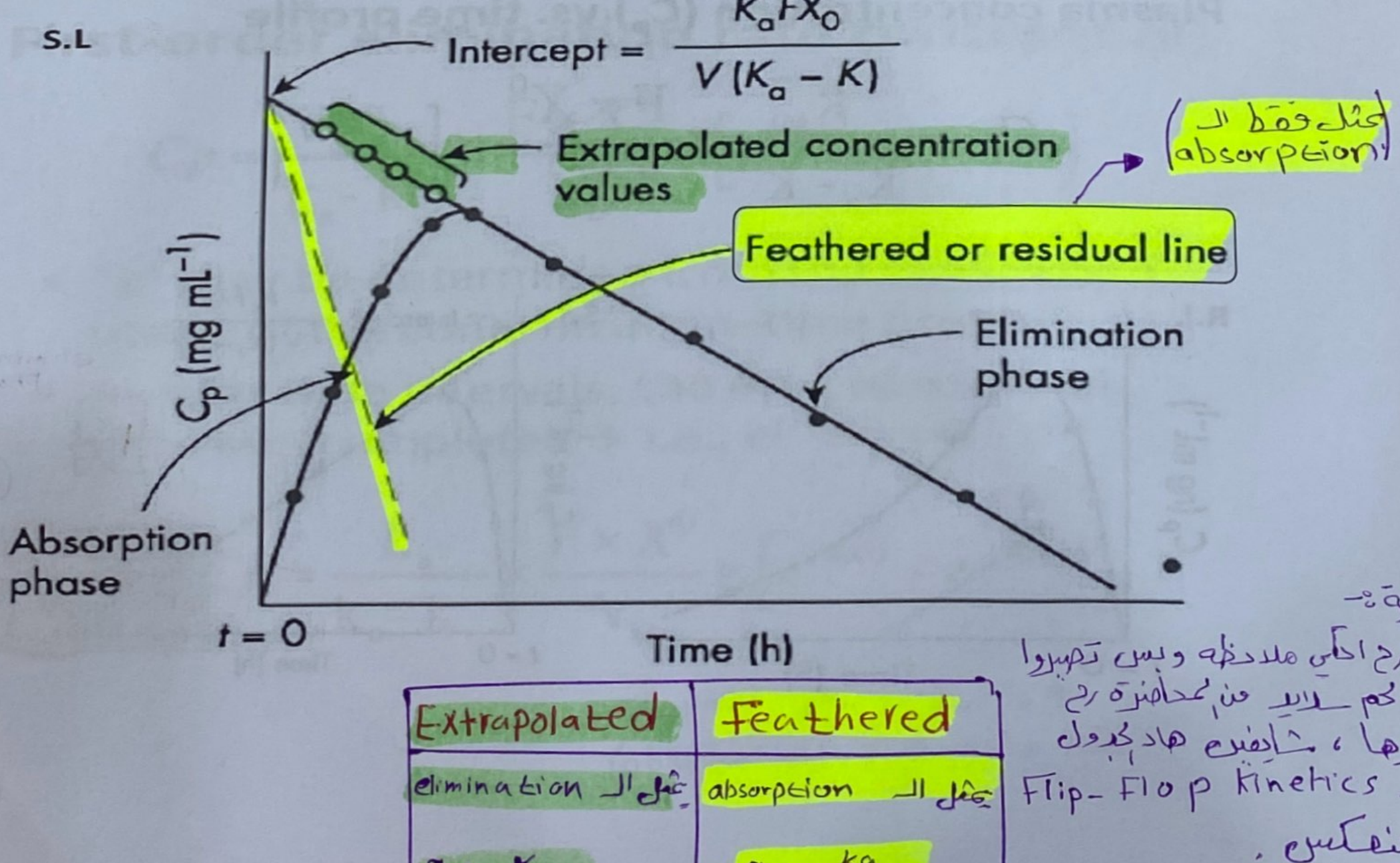
الـ slop فقط يكون (K)

First-order absorption rate constant (k_a)

- "ka" is determined by a method known as **"feathering"="method of residuals" = "curve stripping"**
- Using this profile→→



بس بنقط هاد الخط وبدي أطرح منه القيم
هدول
رح يطلع معي خط اسمه :-
(Residual line) بالانجليزي.



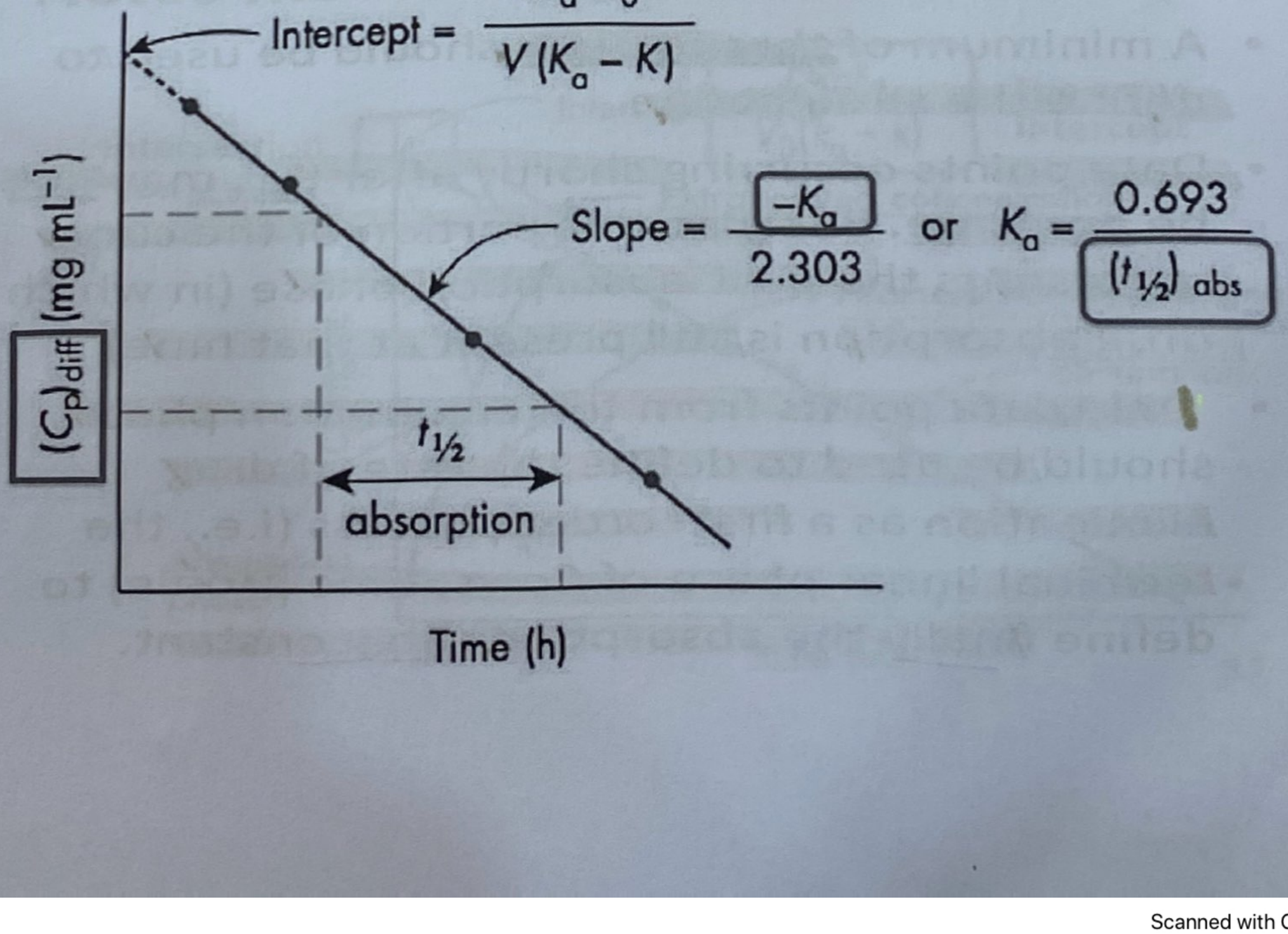
Extrapolated	Feathered
elimination يمثل ال	absorption يمثل ال
Slop = $\frac{K}{2.303}$	Slop = $\frac{ka}{2.303}$

ملاحظة :-
طيب رح احكي ملاحظة وبس تخبروا ع آخر كم سلايد من المحاضرة رح شوفوها ، شايفين هاد الجدول Flip-Flop kinetics بال رح ينعكس .

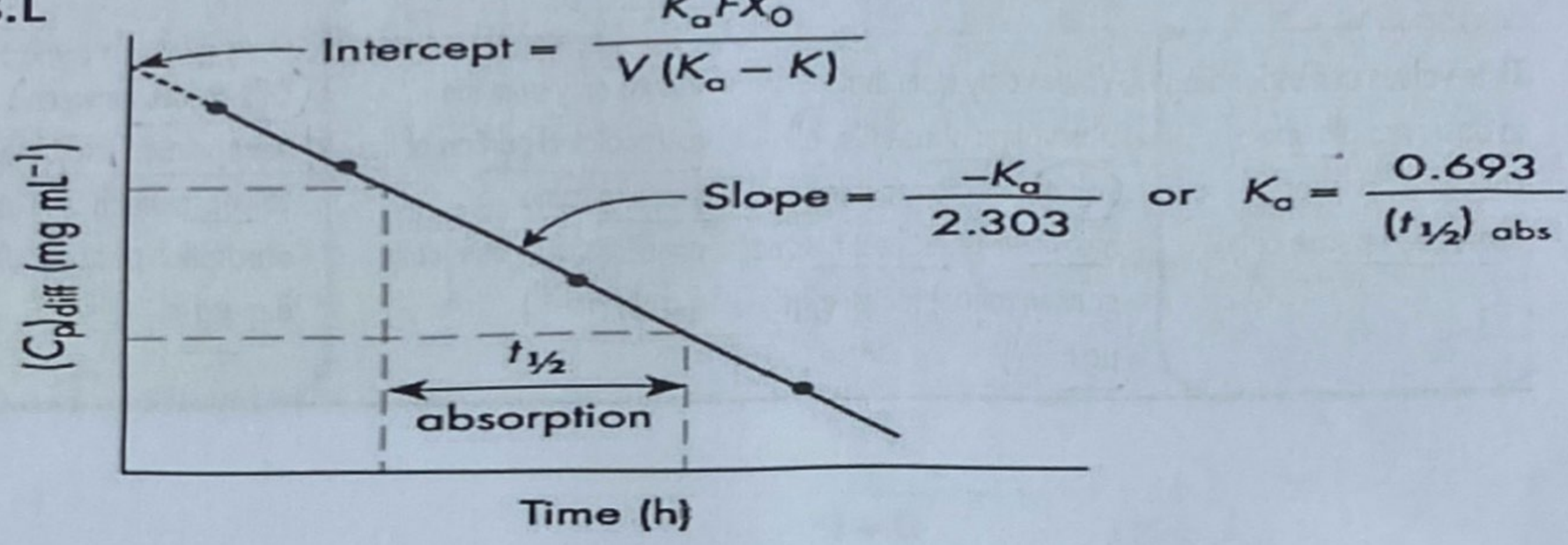
Illustration of the table created for determination of the first-order absorption rate constant K_a

Time (h)	Observed plasma concentration $(C_p)_{obs}$	Extrapolated plasma concentration $(C_p)_{extrap}$	$(C_p)_{diff} = (C_p)_{extrap} - (C_p)_{obs}$
Time values corresponding to observed plasma concentrations for absorption phase only	Values only from the absorption phase (i.e. all values prior to reaching maximum or highest plasma concentration) (units, e.g. $\mu g\ mL^{-1}$)	Values only from the extrapolated portion of the plot of plasma concentration–time (units, e.g. ($\mu g\ mL^{-1}$)	(Differences between) extrapolated and observed values for each time in the absorption phase (units, e.g. $\mu g\ mL^{-1}$)

S.L



$$Cp_{diff} = \frac{k_a F X^0}{(k_a - k) V_D} \times \left(e^{(-ka \times t)} \right)$$



Notes-Method of Residuals:

- A minimum of **three points** should be used to define the straight line
- Data points occurring shortly after t_{max} may **not** be **accurate**. Because this portion of the curve represents the post-absorption phase (in which drug absorption is still present at that time)
- Only data points from the elimination phase should be used to define the rate of drug elimination as a first- order process (i.e., the terminal linear phase of Cp vs. time profile) to define finally the absorption rate constant.

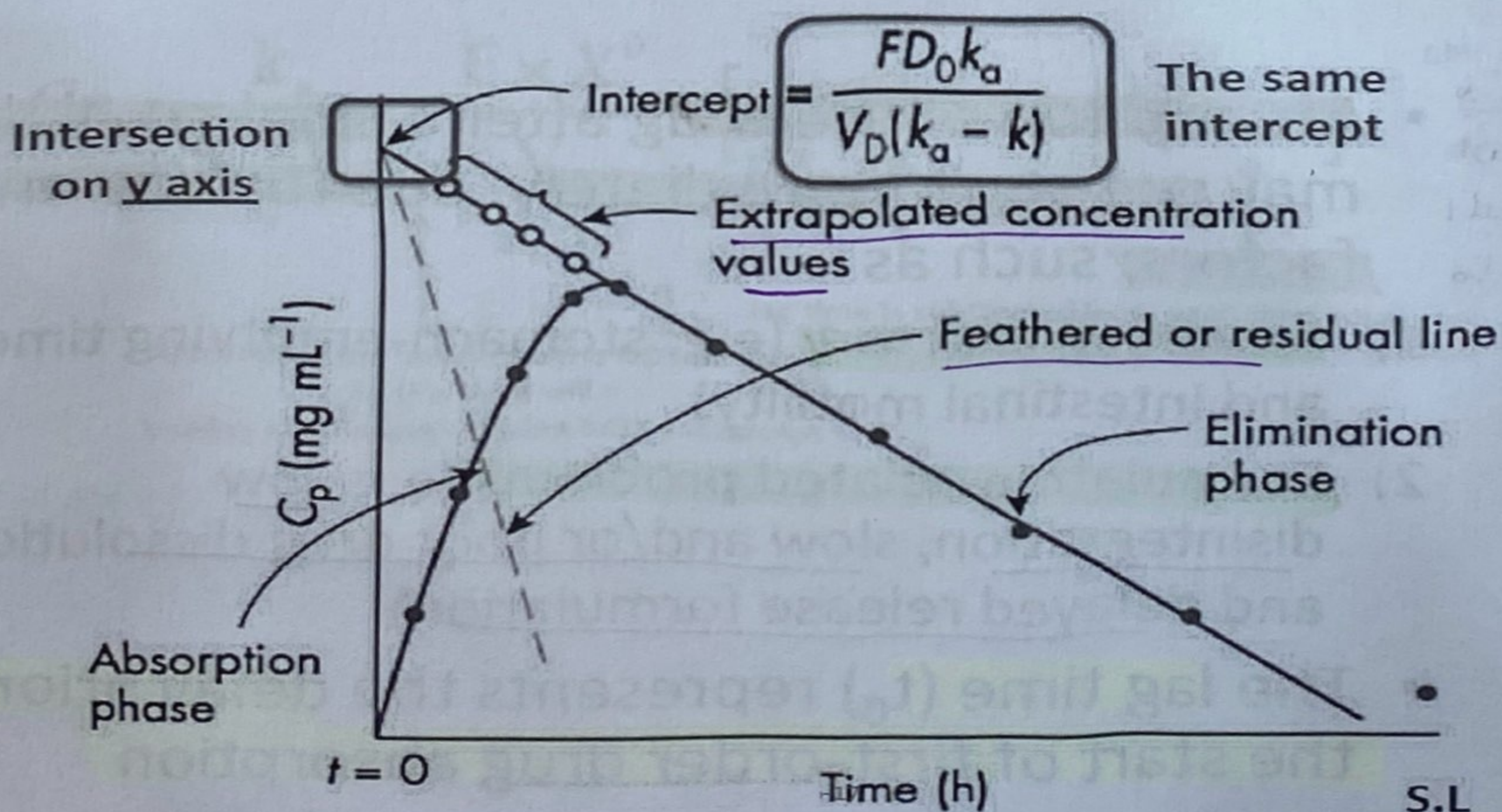
Notes-Method of Residuals:

- This method gives accurate values of k and k_a if one rate constant (k or k_a) is much larger than the other (e.g. $k_a >>> k$) and both absorption and elimination are first order processes

ملاحظة لقدام (أخركم سلايد رح تفهموا).

لهون Flip- Flop Kinetics تكون ← K أعلى من Ka

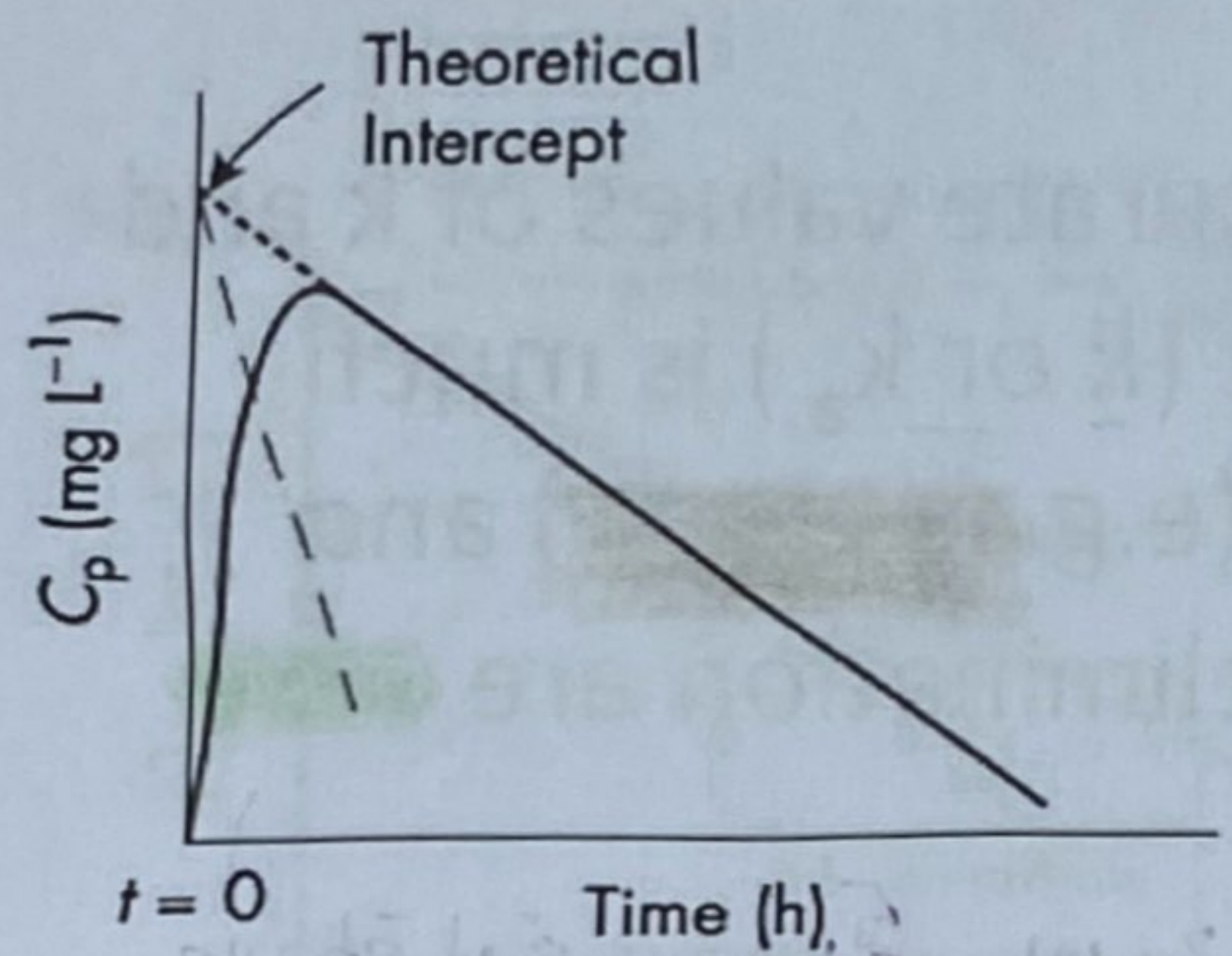
Notes-Method of residuals: (Cont'd)

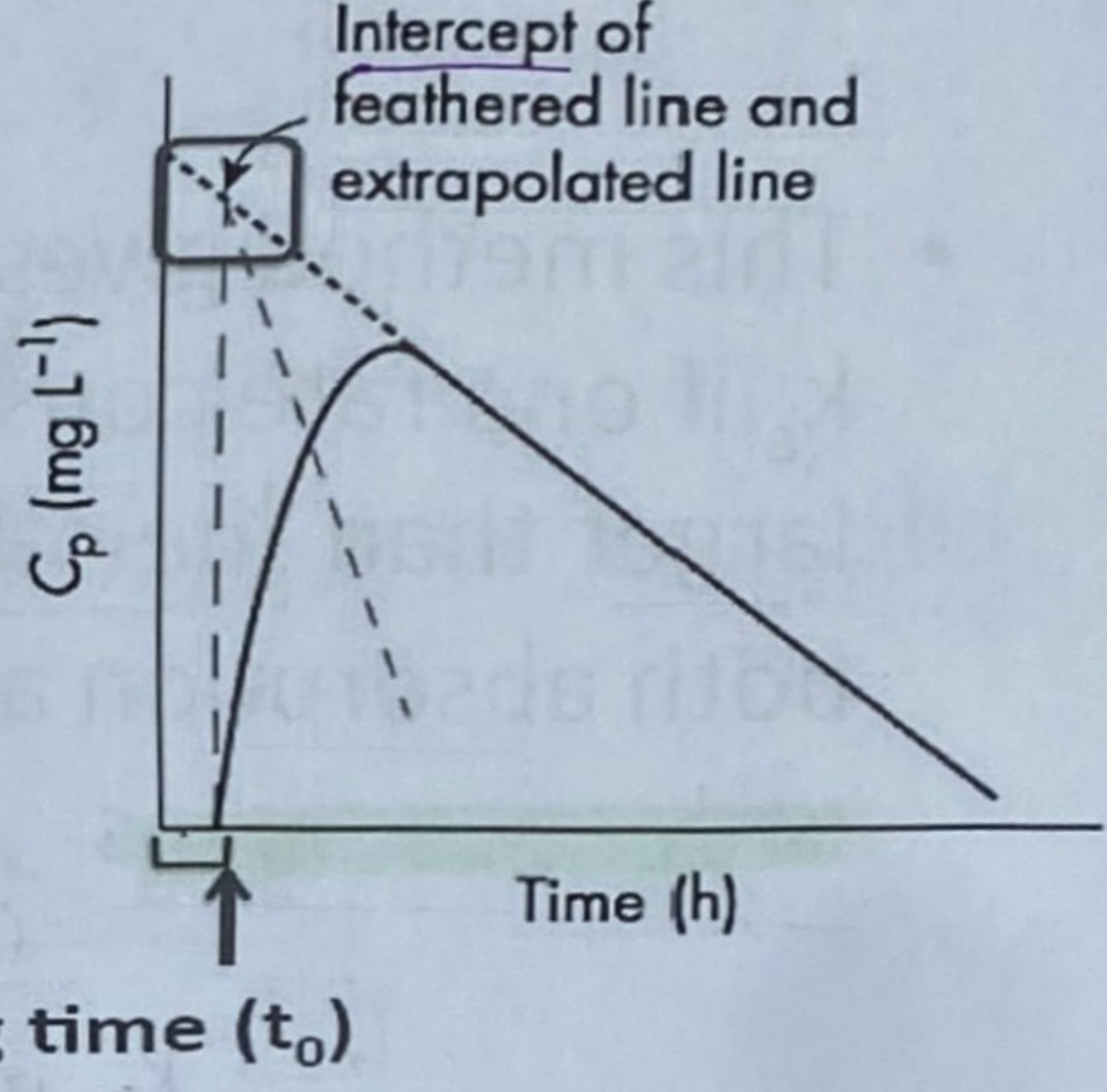


* الأدوية الي بتتناول (delayed release drugs) بتمر ب (gastric emptying) → (Lag time)

(Lag time) ↓ هو يعني ما بلش من عند curve of absorption

Lag time (t_0)





Lag time (t_0)- Cont'd

في عوامل بتخلي انه ما يبلش عندي الامتصاص بعد ما أخذ ال dose → orally

- Absorption of the drug after a single oral dose may not start immediately, due to different factors; such as

1) Physiologic factors (e.g. stomach-emptying time and intestinal motility)
2) Formulation-related problems (e.g. low disintegration, slow and/or poor drug dissolution, and delayed release formulation)

- The lag time (t_0) represents the delay prior to the start of first-order drug absorption

Lag time (t_0) - Cont'd

Be careful!

- The lag time (t_0): represents the beginning of drug absorption
- Onset time of action: represents the time required for the drug to reach minimum effective concentration

Lag time (t_0) - Cont'd

$$Cp = \frac{k_a}{k_a - k} \times \frac{F \times X^0}{V_D} \times \left[e^{(-kx(t-t_0))} - e^{(-kax(t-t_0))} \right]$$

عشان أطرح الـ time الزيادة اللي كان بالدراية وهي لفترة اللي ما صار فيها لزوار absorption

يعني يكون الدواء لسا خاش أو انه تكسر بس ماصار له absorption.

Remember: the Intersection is NOT on y axis
So this term will =
y-value at intersection point NOT y-intercept

lag time is subtracted from each time point

طيب ، الـ "Flip - Flop Kinetics" عكس اللي أخدنا قبل كدة ! ☺

قبل كنا نحكي اول ما يبلش الدواء يكون عندي absorption rate constant أعلى من elimination rate constant

هون العكس :- اول ما يبلش

[absorption rate constant] أقل [elimination rate constant]

Flip-Flop kinetics

- Oral absorption kinetics often describe the **usual** case in which the absorption rate constant is greater than the elimination rate constant:

زي ما حكينا بداية المحاضرة ،

$$k_a > k$$

In which the absorption process is faster than elimination process

$$t_{0.5\ (abs)} < t_{0.5\ (Elim)}$$

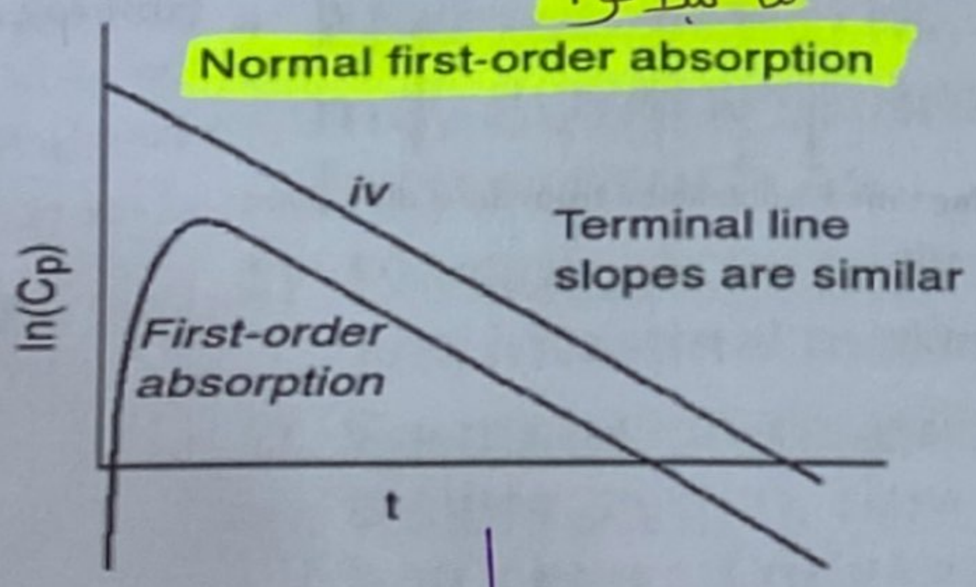
Shorter

* يعني تكون الـ K أعلى من Ka ـــه بعدين (Flip-Flop Kinetics)

Distinguishing between Normal and Flip-Flop kinetics

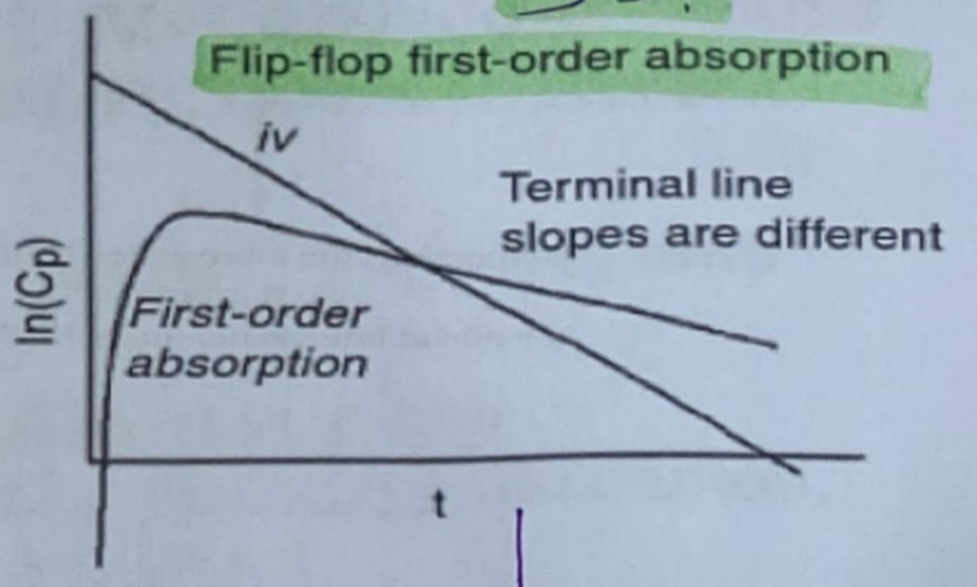
ما تبلاقوا

Normal first-order absorption



بتلاقوا

Flip-flop first-order absorption



IV bolus data is needed to differentiate between Normal and Flip-Flop kinetics

absorption rate constant أكبر elimination rate constant	elimination rate constant أكبر absorption rate constant
K أكبر من Ka	Ka أكبر من K

Flip-Flop kinetics

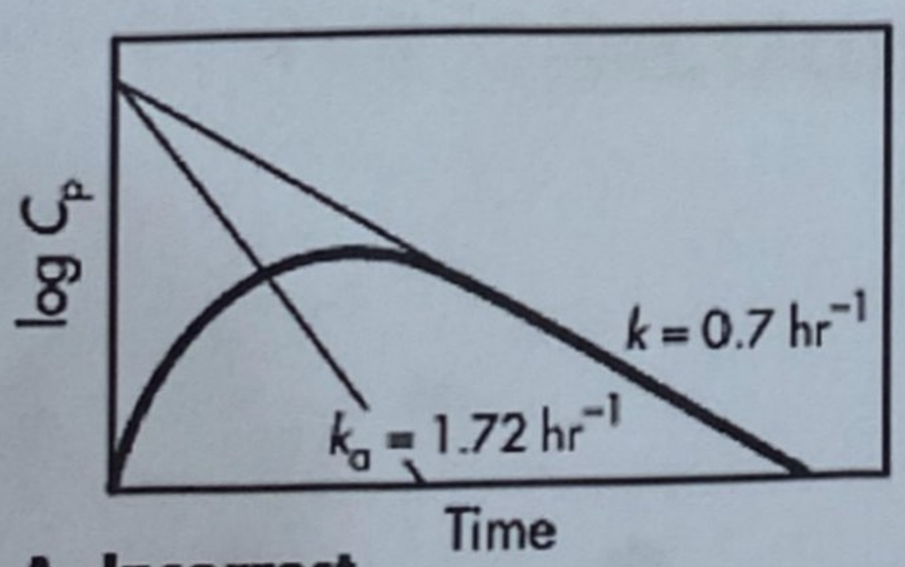
- **Flip-flop** kinetics is **an exception** to that usual case
- For drugs with slow first-order absorption process (e.g., certain types of sustained- release and controlled-release formulations)
- When the elimination rate constant starts to be greater than the absorption rate constant

(k > ka) → Flipped condition → "Flip-Flop kinetics"

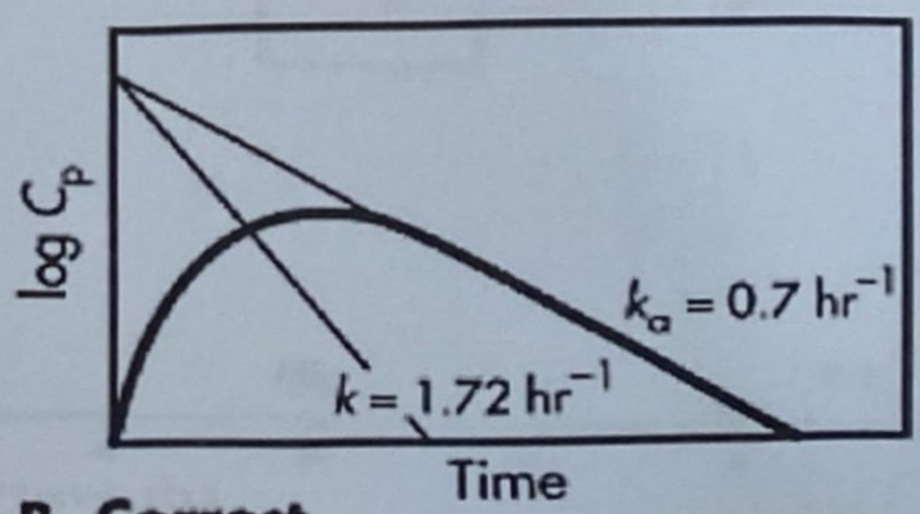
- Then, as the terminal linear slope of plasma drug concentration vs. time (S.L graph) → always represents the slower process → This slope represents the absorption rate constant
- The slope of the feathered line will represent the elimination rate constant

مش داخله

Flip-Flop kinetics →



A. Incorrect



B. Correct