

Lab 5

Determination of Pharmacokinetic Parameters from Plasma Data

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Introduction to Pharmacokinetic Parameters

Most pharmacokinetic parameters can be reliably measured from plasma data following either **oral** or **intravenous bolus** administration.

These parameters form the foundation of **drug therapy individualization** and **clinical decision-making** in pharmacy practice.

AUC

Area under the curve - total drug exposure

Clearance (Cl)

Volume of plasma cleared per unit time

Elimination Rate Constant (k)

Rate at which drug leaves the body

Volume of Distribution (Vd)

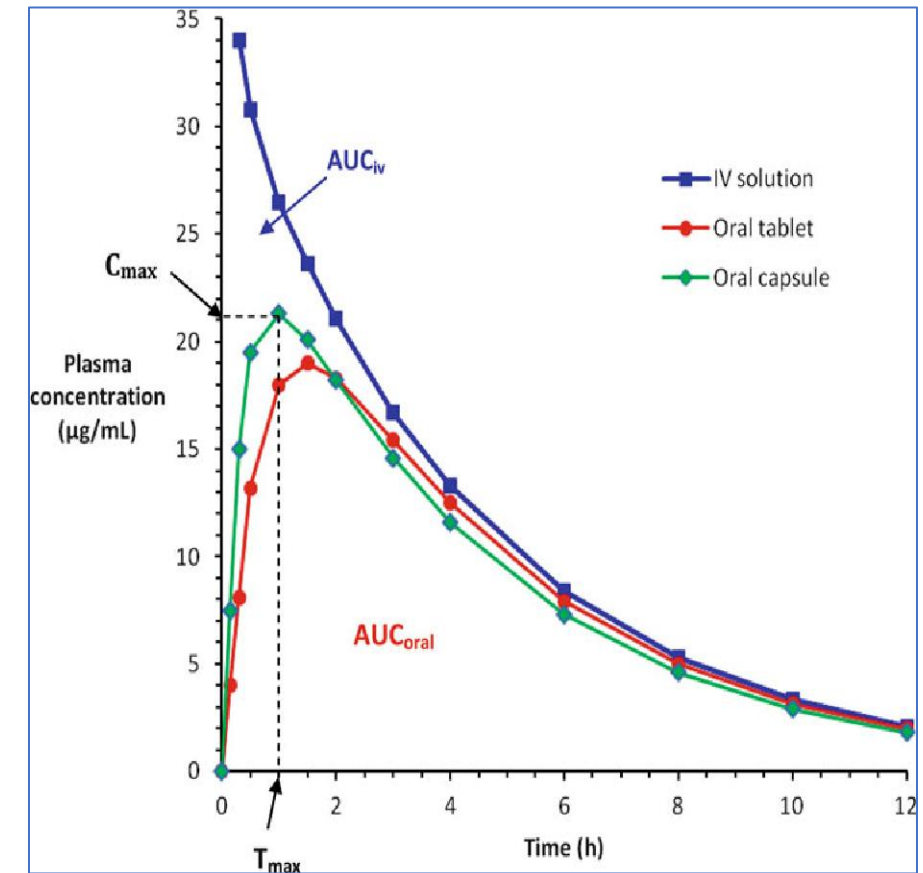
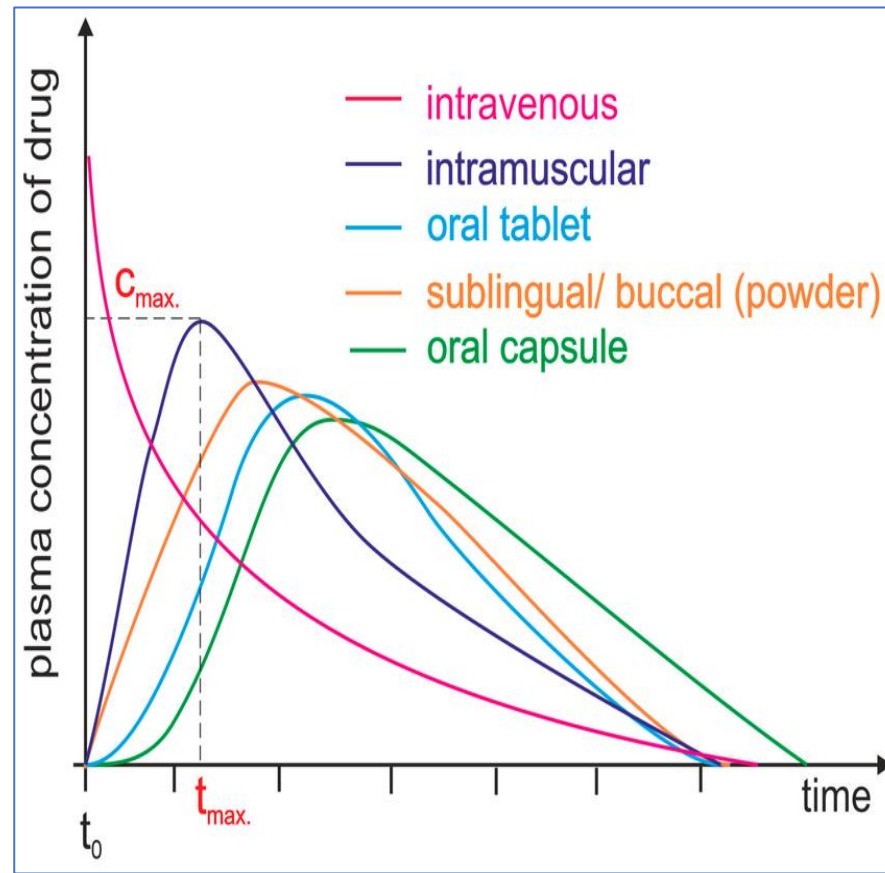
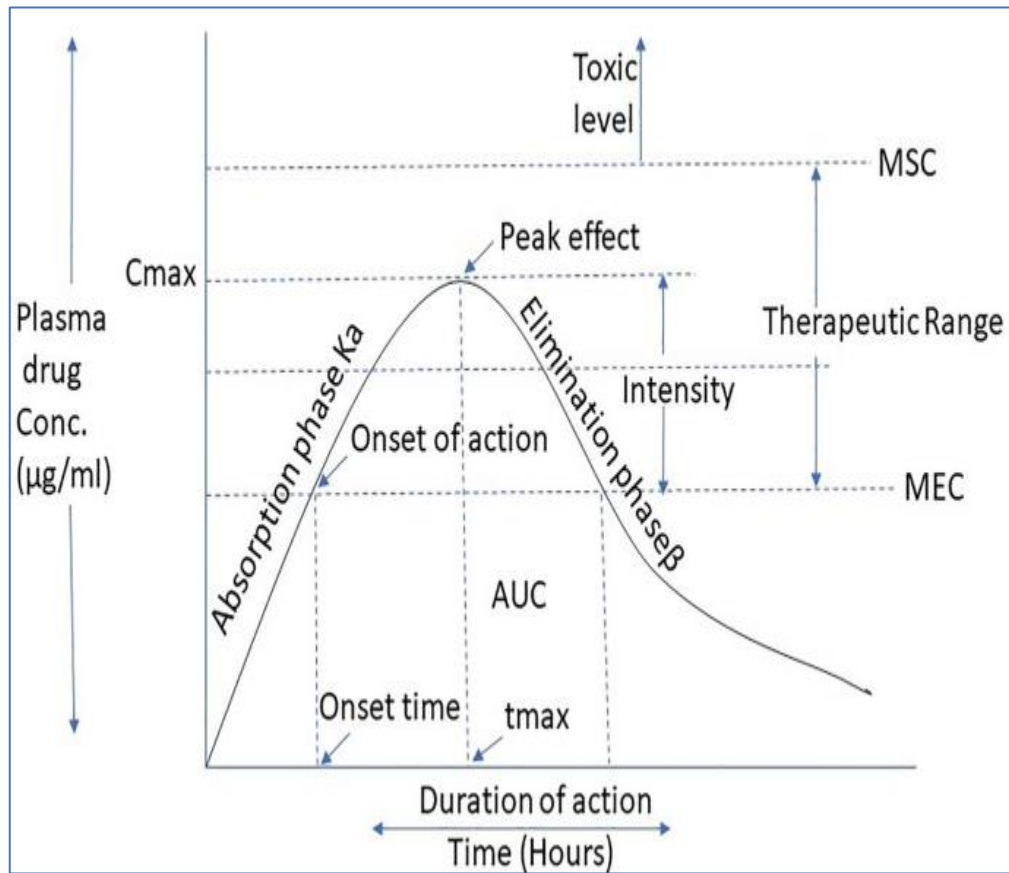
Theoretical volume drug distributes into

Bioavailability (F)

Fraction of dose reaching systemic circulation

Half-Life ($t_{1/2}$)

Time for plasma concentration to decrease by 50%

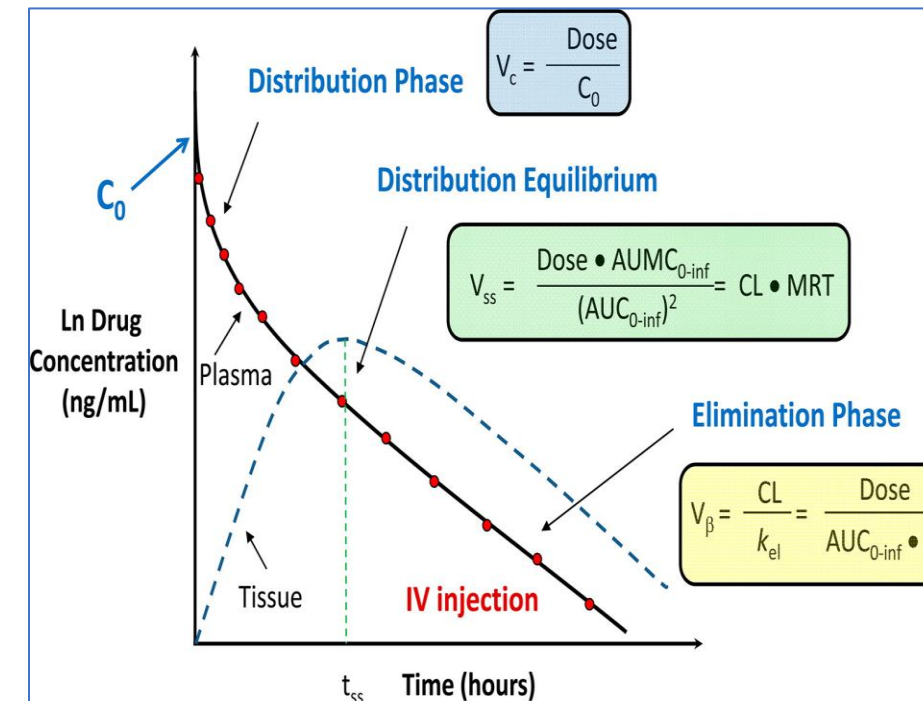
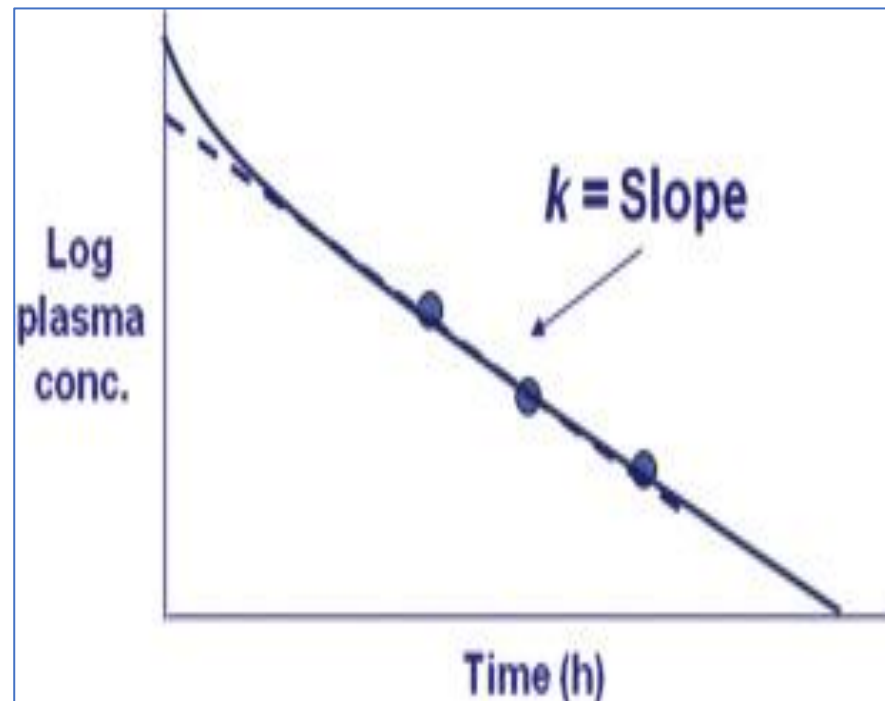


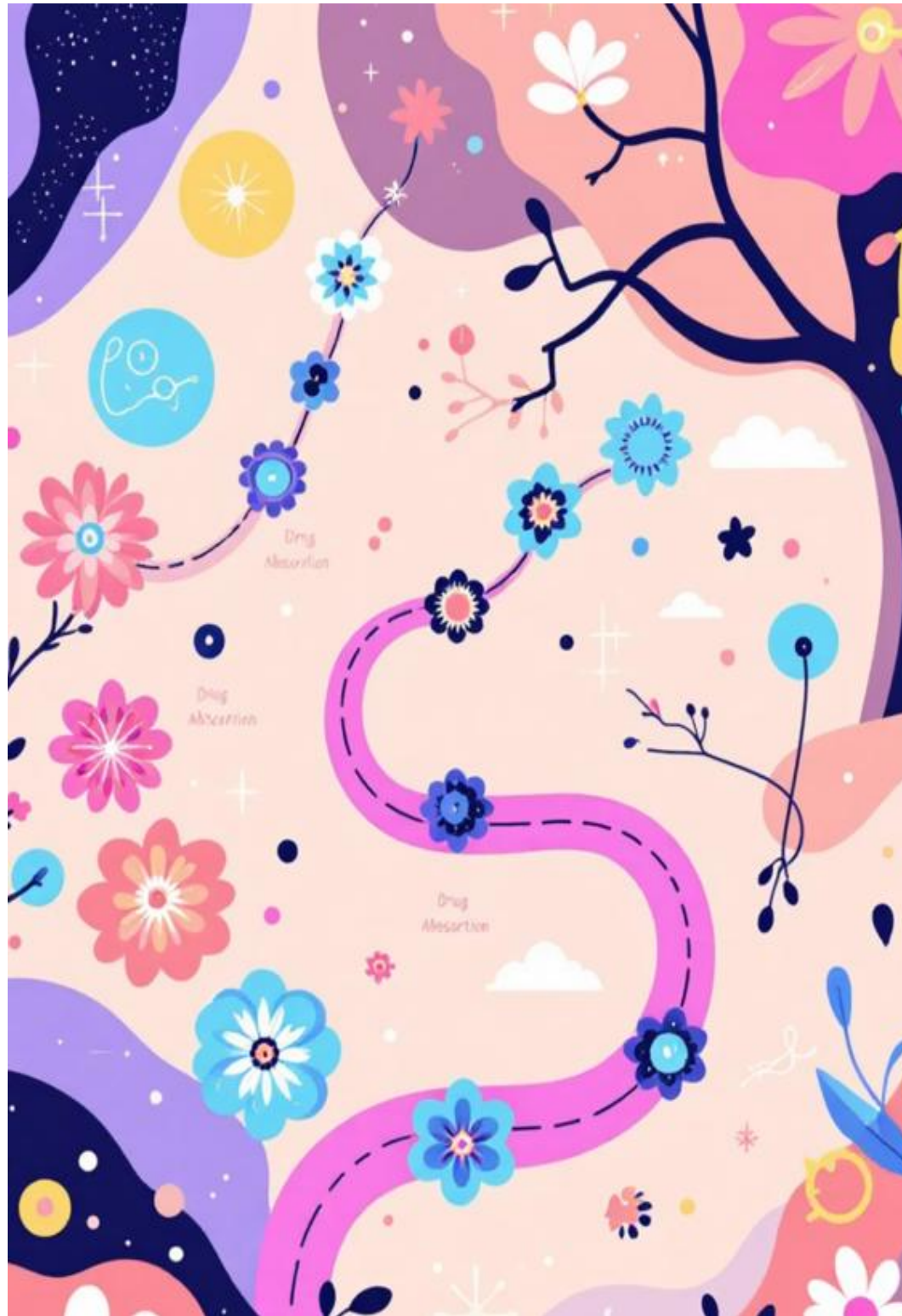
DRUG ELIMINATION

$$Cl = V_D \cdot k$$

$ml \cdot min^{-1} = ml \cdot min^{-1}$

Volume of Distribution: V_D
 Elimination Rate Constant: k





Understanding Bioavailability

- **Bioavailability** is a critical pharmacokinetic parameter that quantifies both the **rate** and **extent** (absolute amount) of therapeutically active drug that reaches the systemic circulation after administration.
- It reflects the fraction of an administered dose that becomes available in the bloodstream, ranging from **0 to 1** (or 0-100%).
- This parameter is essential for understanding drug absorption differences between routes of administration and for making informed dosing adjustments.

Key Point: Complete bioavailability ($F = 1.0$) occurs with **IV administration**, making it the **reference standard for comparing other routes**.

Area Under the Curve (AUC): The Complete Picture

The Area Under the Curve (AUC) represents the **total drug exposure over time** and is calculated from time zero to infinity ($0 \rightarrow \infty$).

AUC : captures all plasma concentrations, including **trace amounts** that persist long after initial administration.

1 Why Extend to Infinity?

After each elimination half-life ($t_{1/2}$), the remaining concentration is halved: 100 mg \rightarrow 50 mg \rightarrow 25 mg \rightarrow 12.5 mg \rightarrow 6.25 mg...

The drug never completely leaves the body; trace amounts continue to decline asymptotically toward zero.

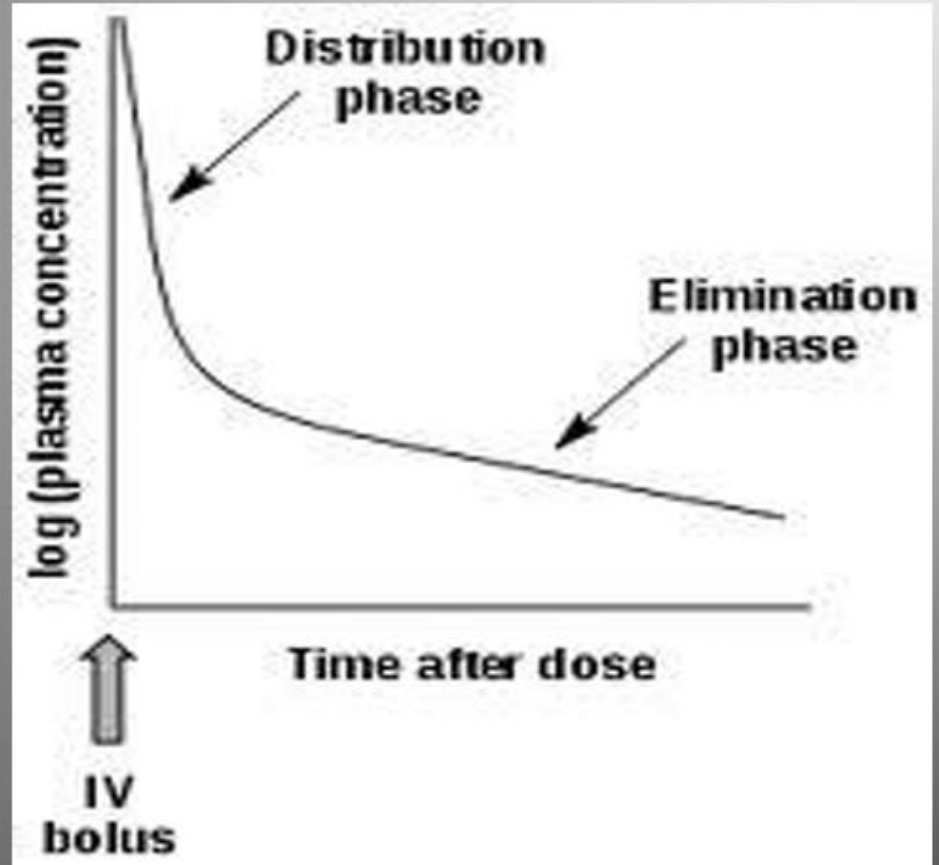
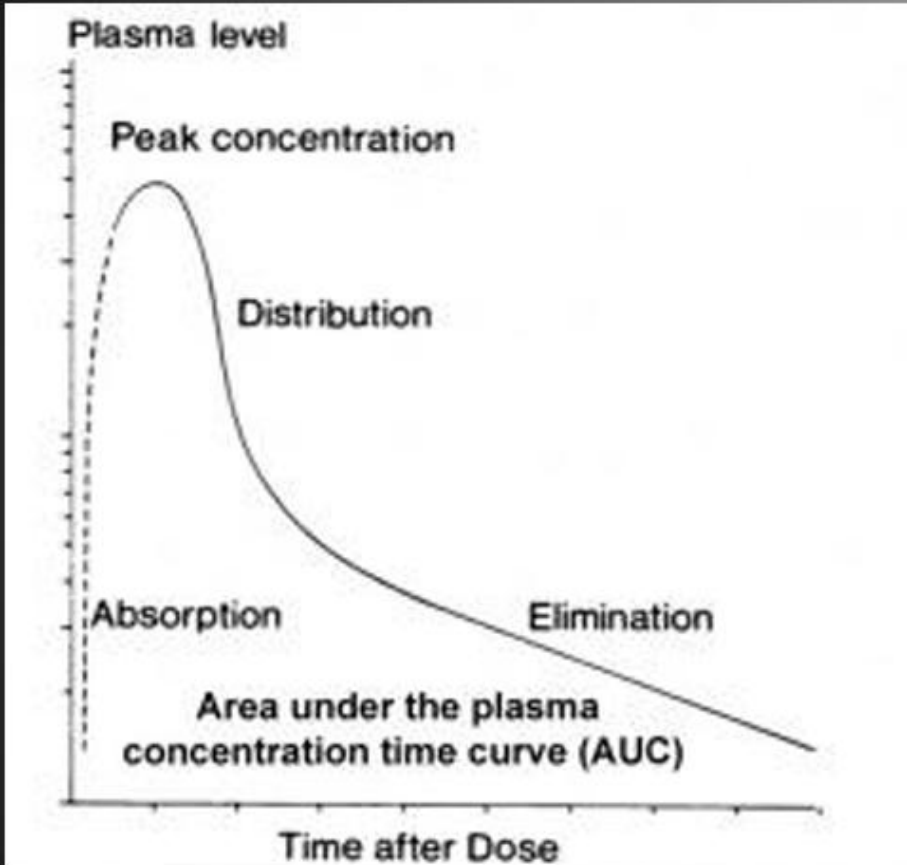
2 Practical Calculation

- AUC is divided into two components: AUC from 0 to the last measurable time point (using trapezoidal rule),
- Plus AUC from the last point to infinity (calculated using the terminal elimination rate constant). This depends on metabolism and excretion.

- $$K_{el} = \frac{Cl}{V_d}$$

3 Clinical Significance

- AUC correlates directly with systemic exposure and is essential
- **bioequivalence studies,**
- **dose optimization**
- **and predicting drug-drug interactions.**



Concept Keys: Fundamental Distinctions in Pharmacokinetics (Distribution)

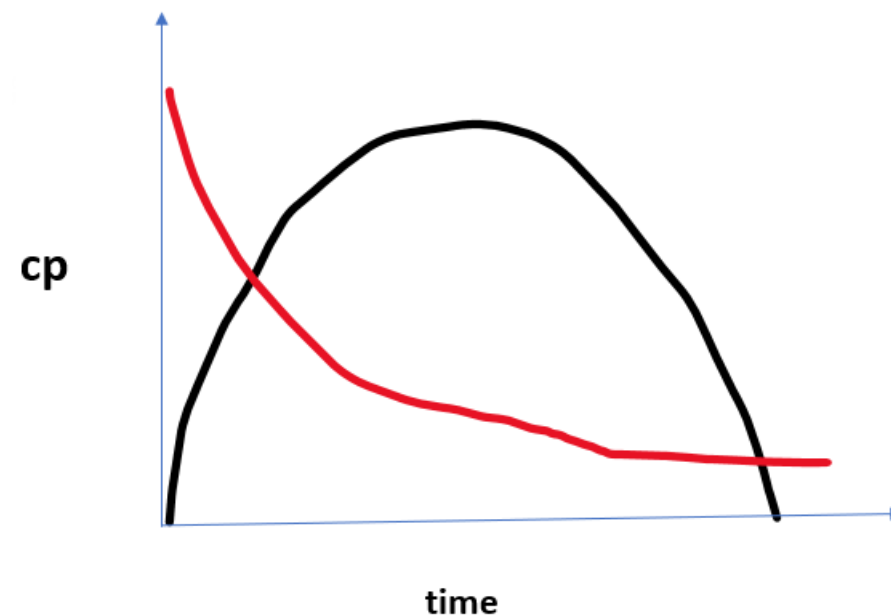


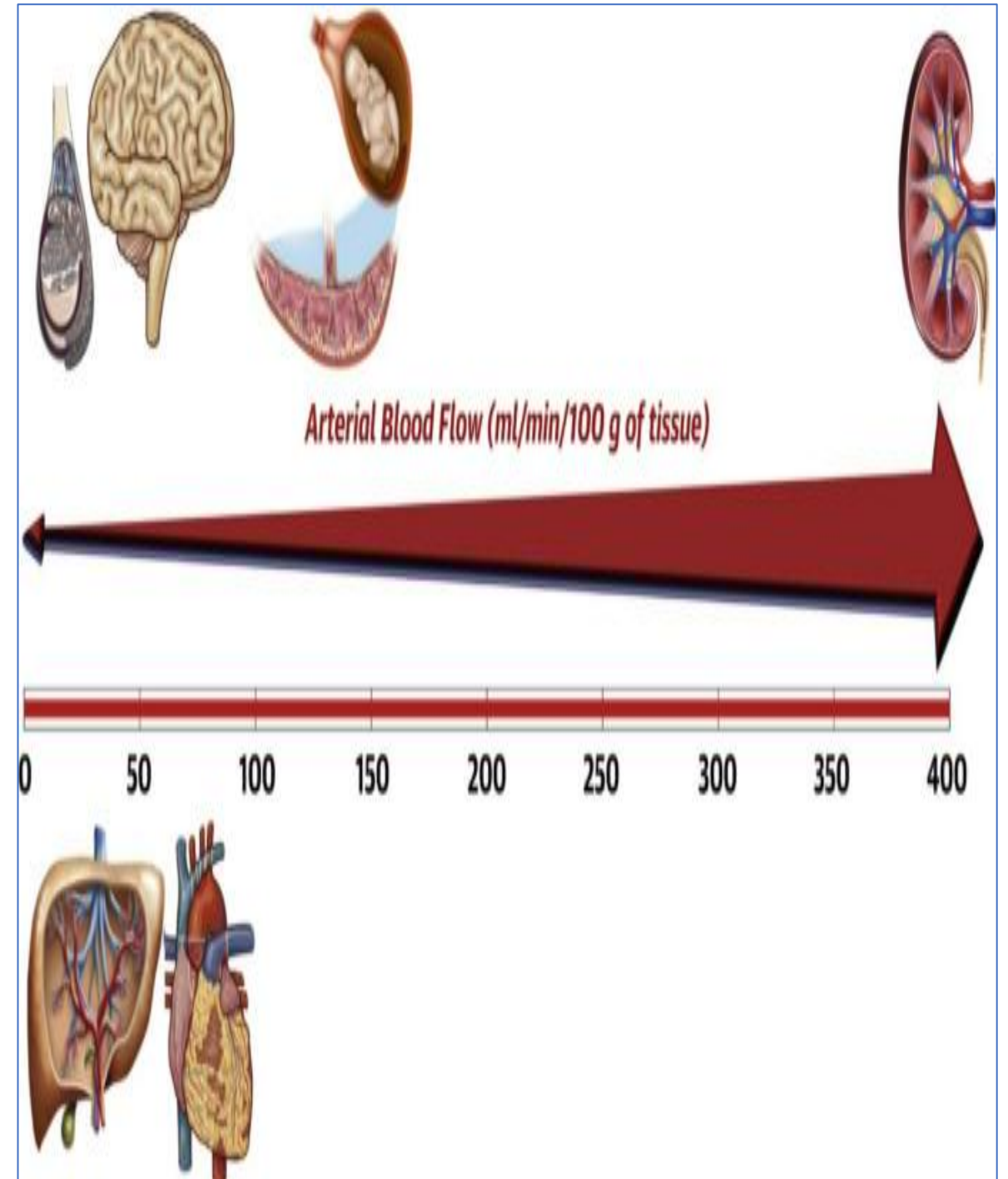
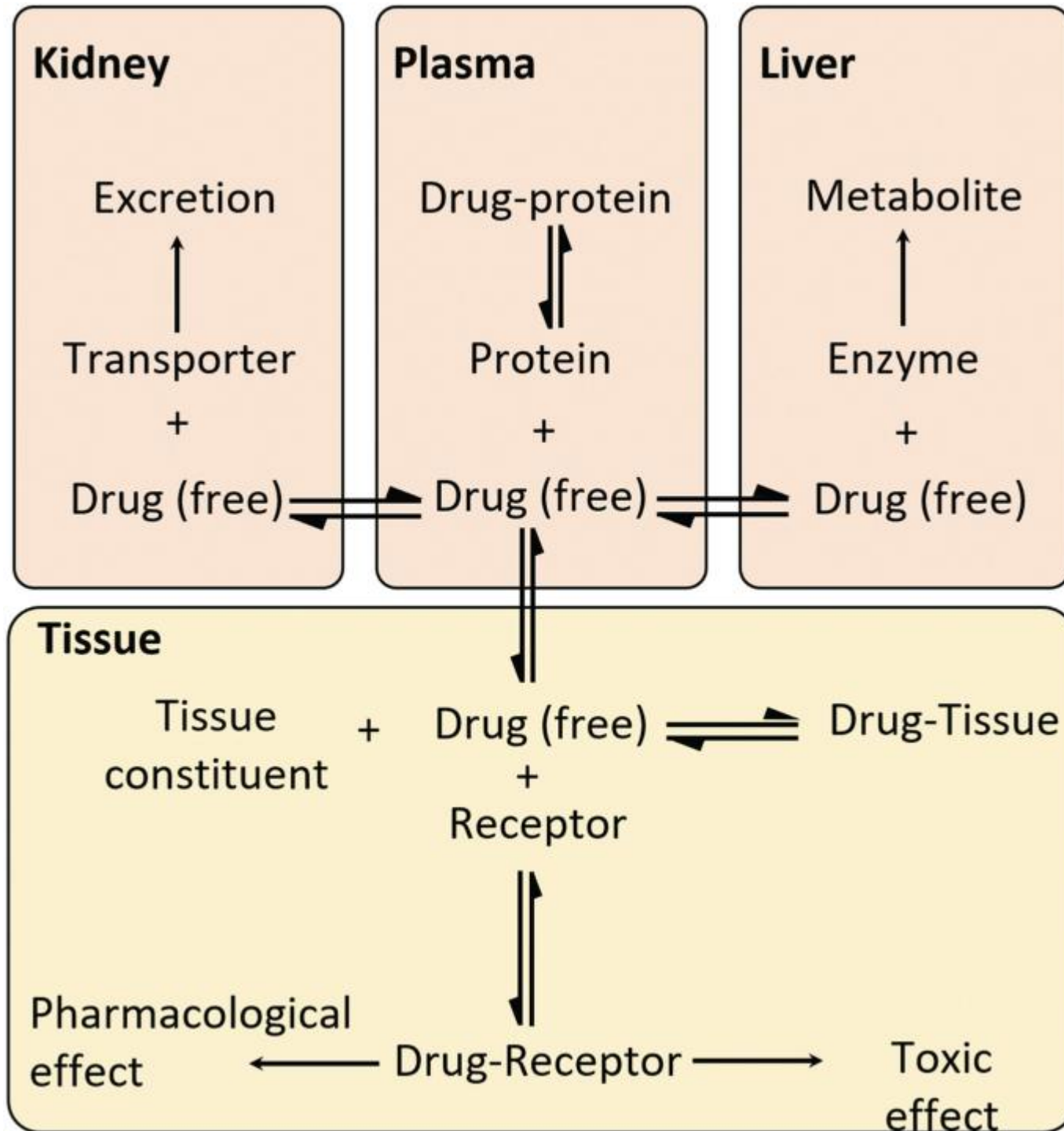
Oral vs. IV Administration: Differences in absorption kinetics and peak concentration patterns affect parameter estimation and clinical outcomes.

One-Compartment Model: Assumes the body acts as a single, homogeneous unit with uniform drug distribution.

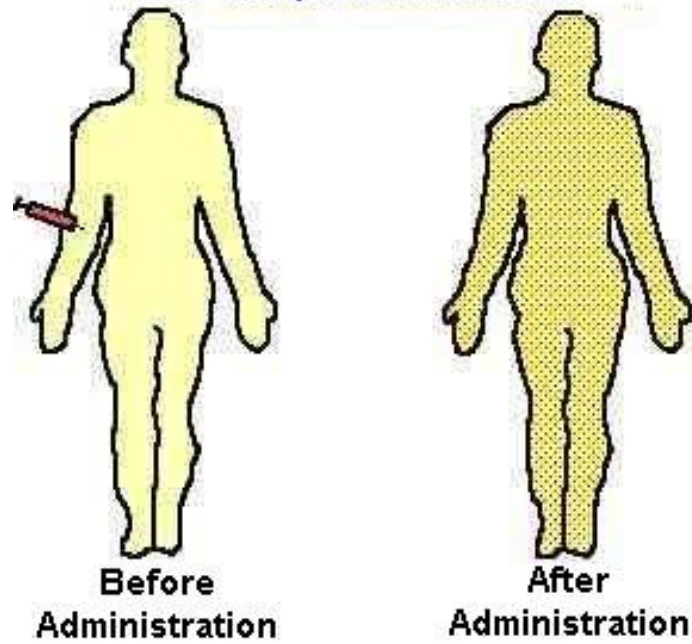
Two-Compartment Model: Recognizes central and peripheral compartments with different drug concentrations and kinetics.

ADME Processes: Absorption, Distribution, Metabolism, and Excretion determine drug behavior and plasma concentrations.

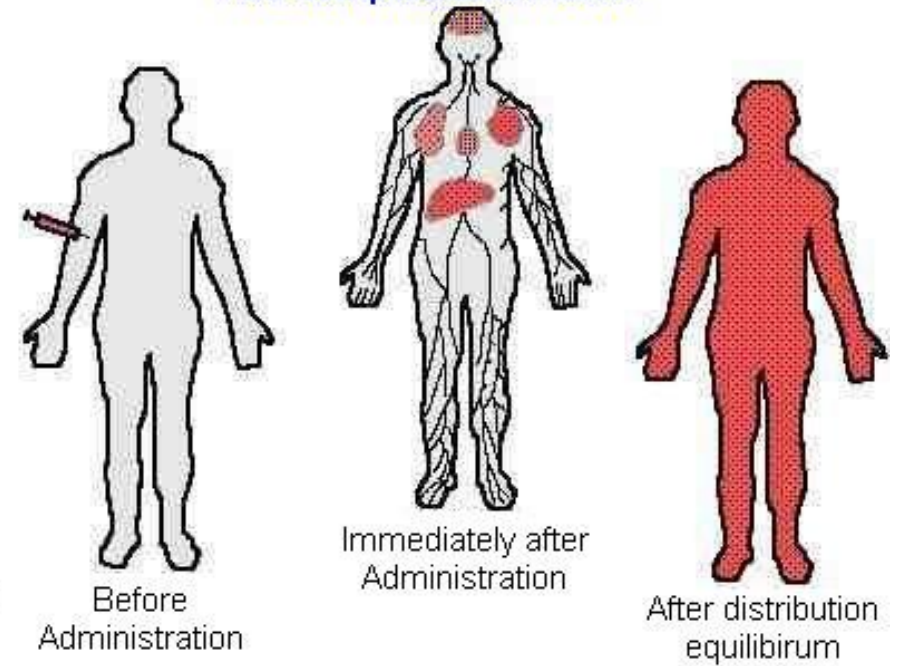




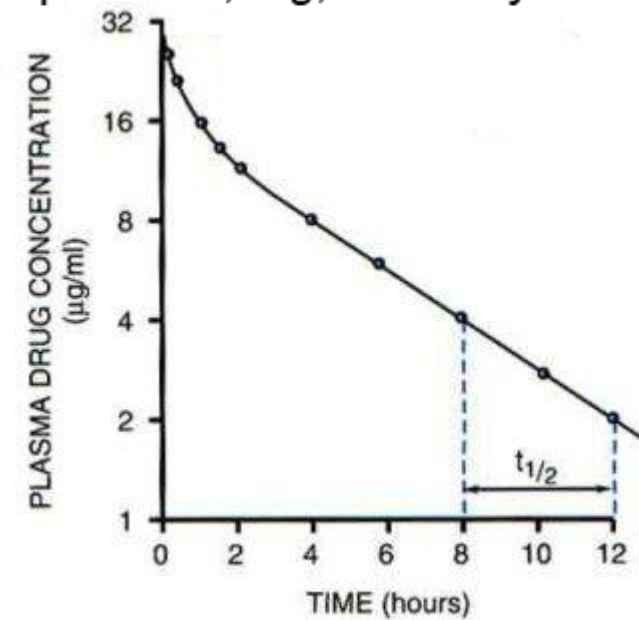
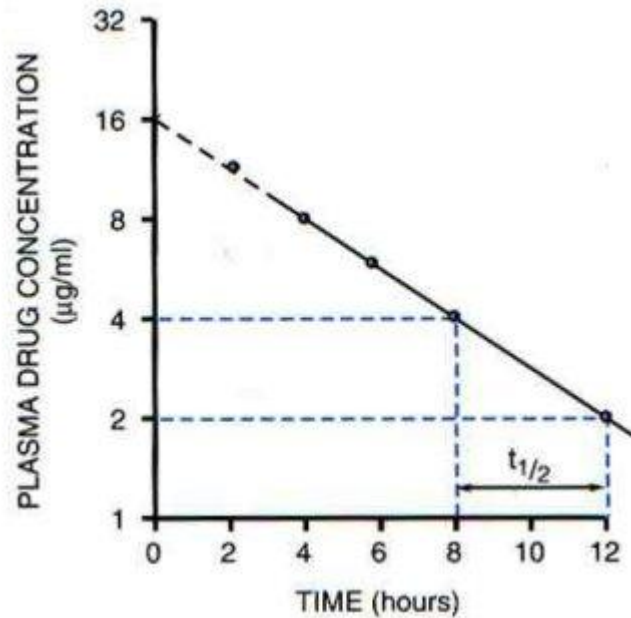
One compartment model



Two compartment model

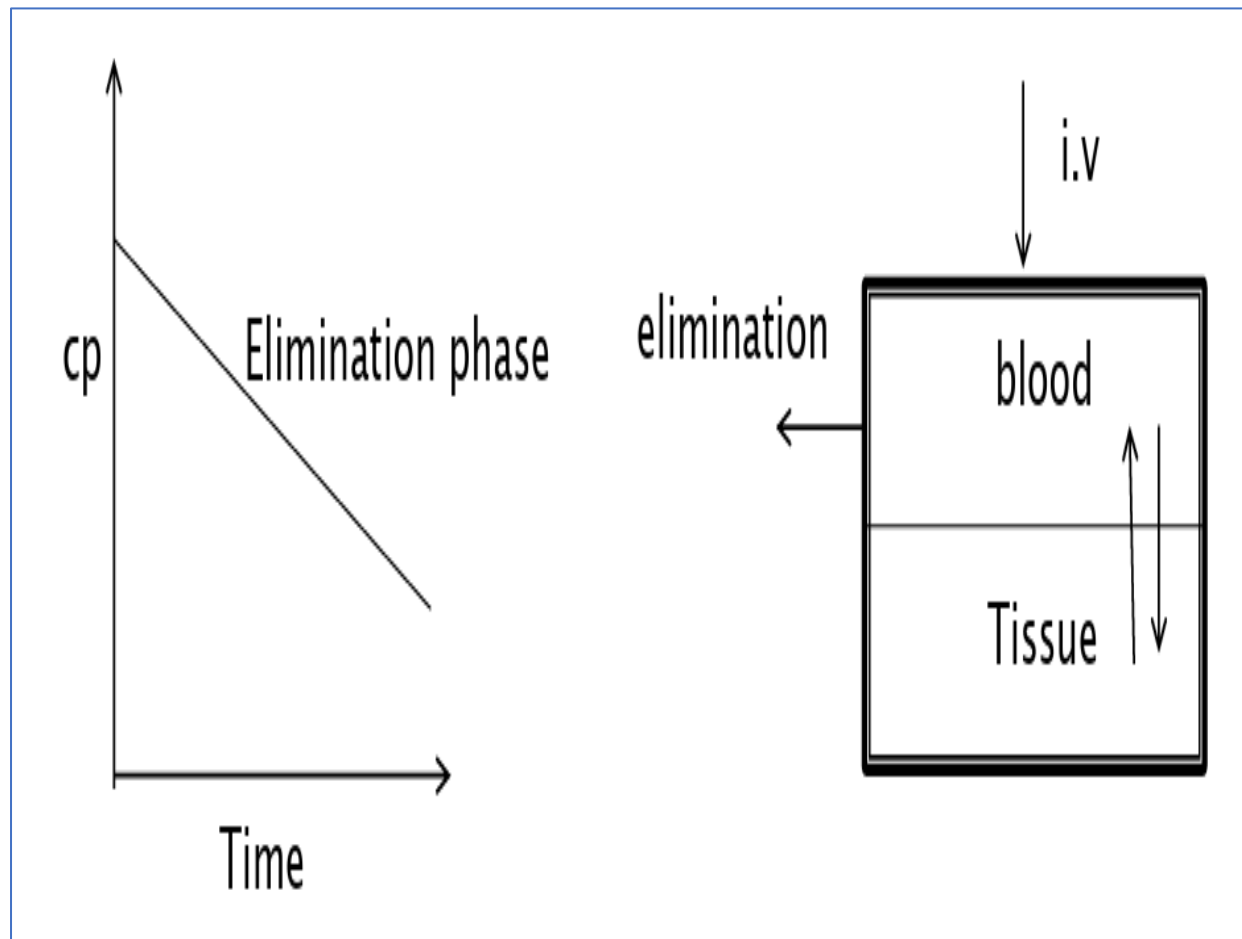


- A **one-compartment model** may be used for drugs which rapidly equilibrate with the tissue compartment, e.g, aminoglycosides.
- A **two-compartment model** should be used for drugs which slowly equilibrate with the tissue compartment, e.g, vancomycin

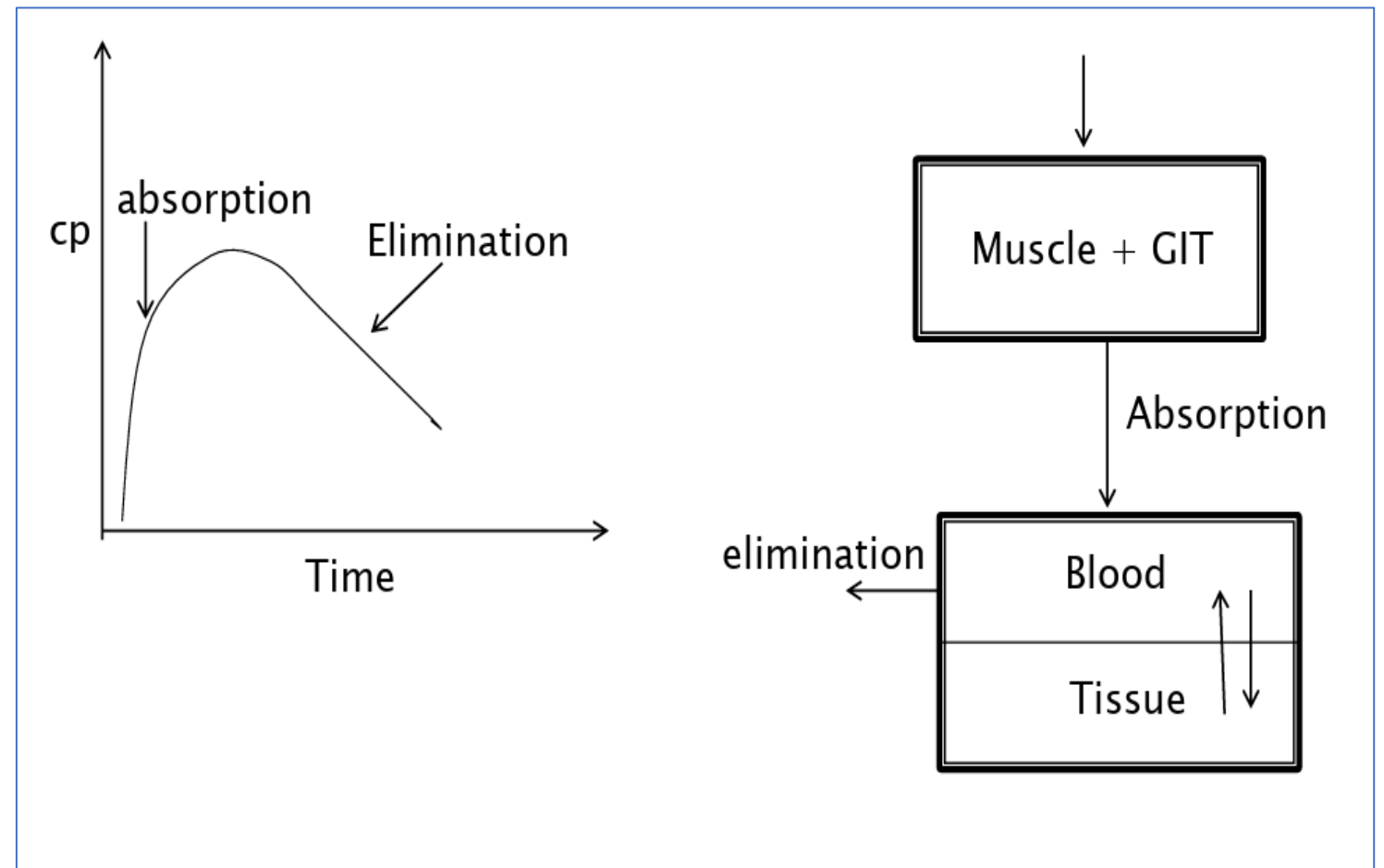


One compartment model (It seems that the drug distribution is very rapid, and we can't notice the distribution phase).

I.V. bolus

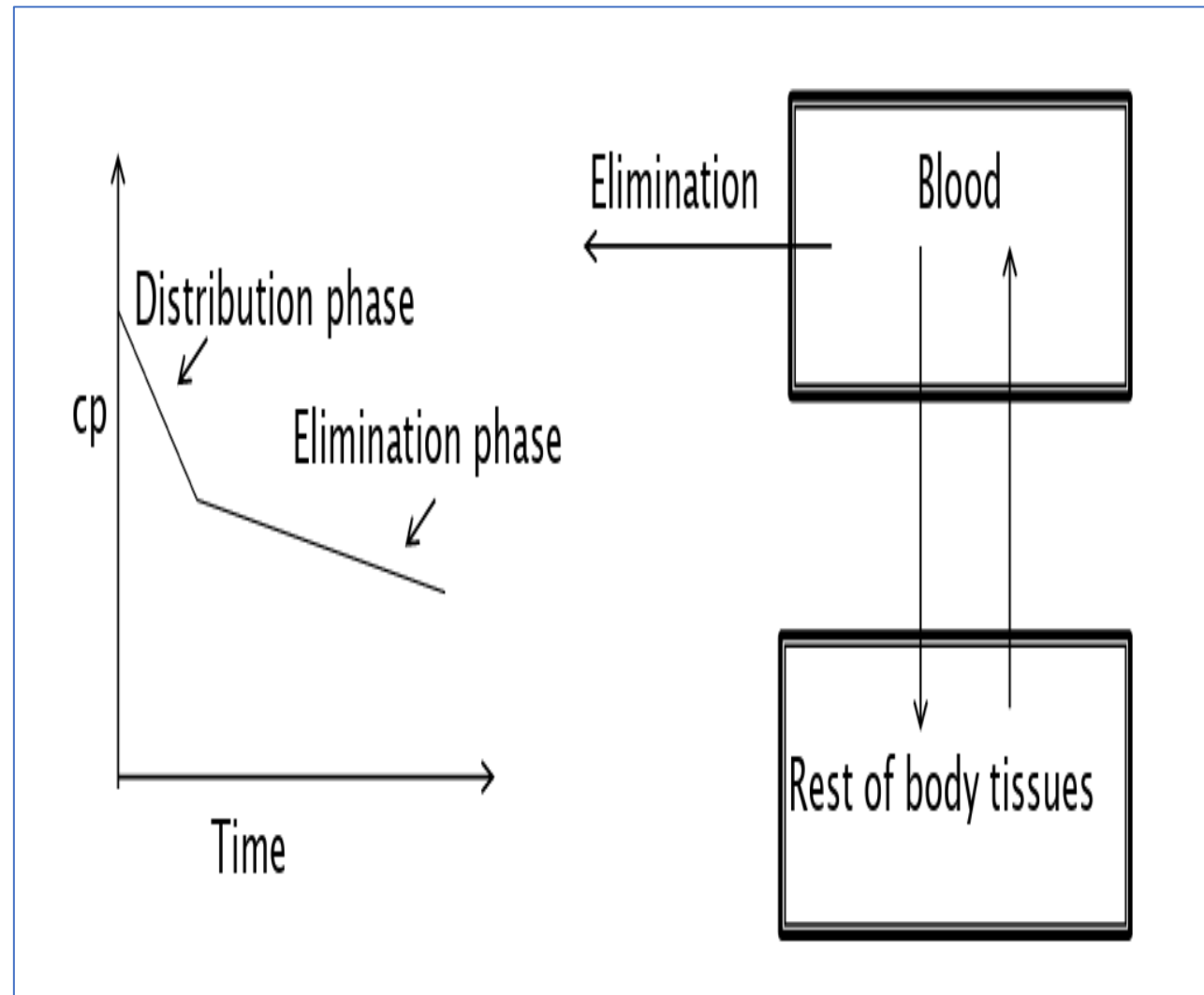


1st order absorption (extra vascular)

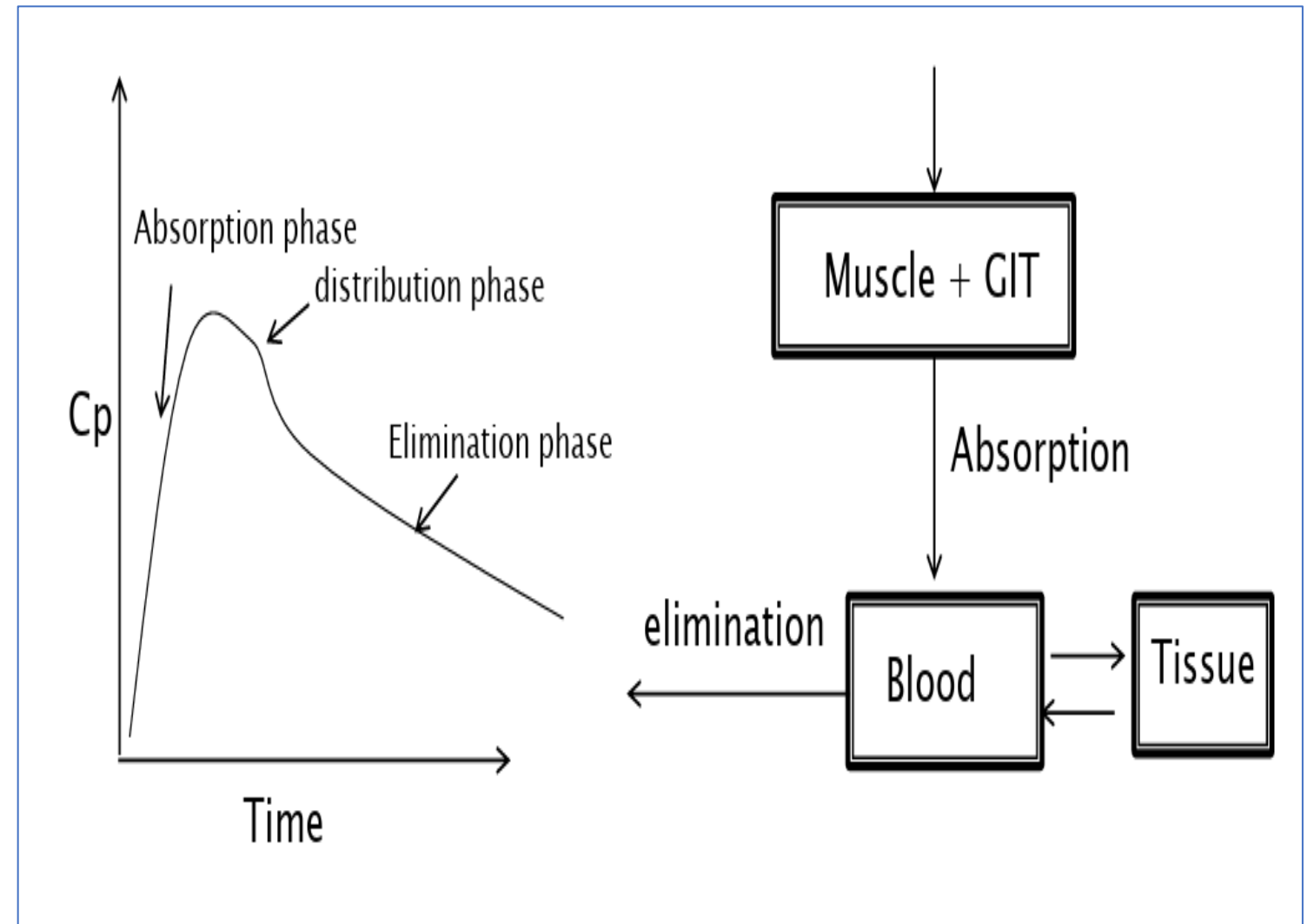


Two-compartment model (well be a clear distribution phase).

I.V. bolus



1st order absorption (extra vascular)



Methods for estimation of AUC for IV bolus - one compartment model

- **1- Residual method :**

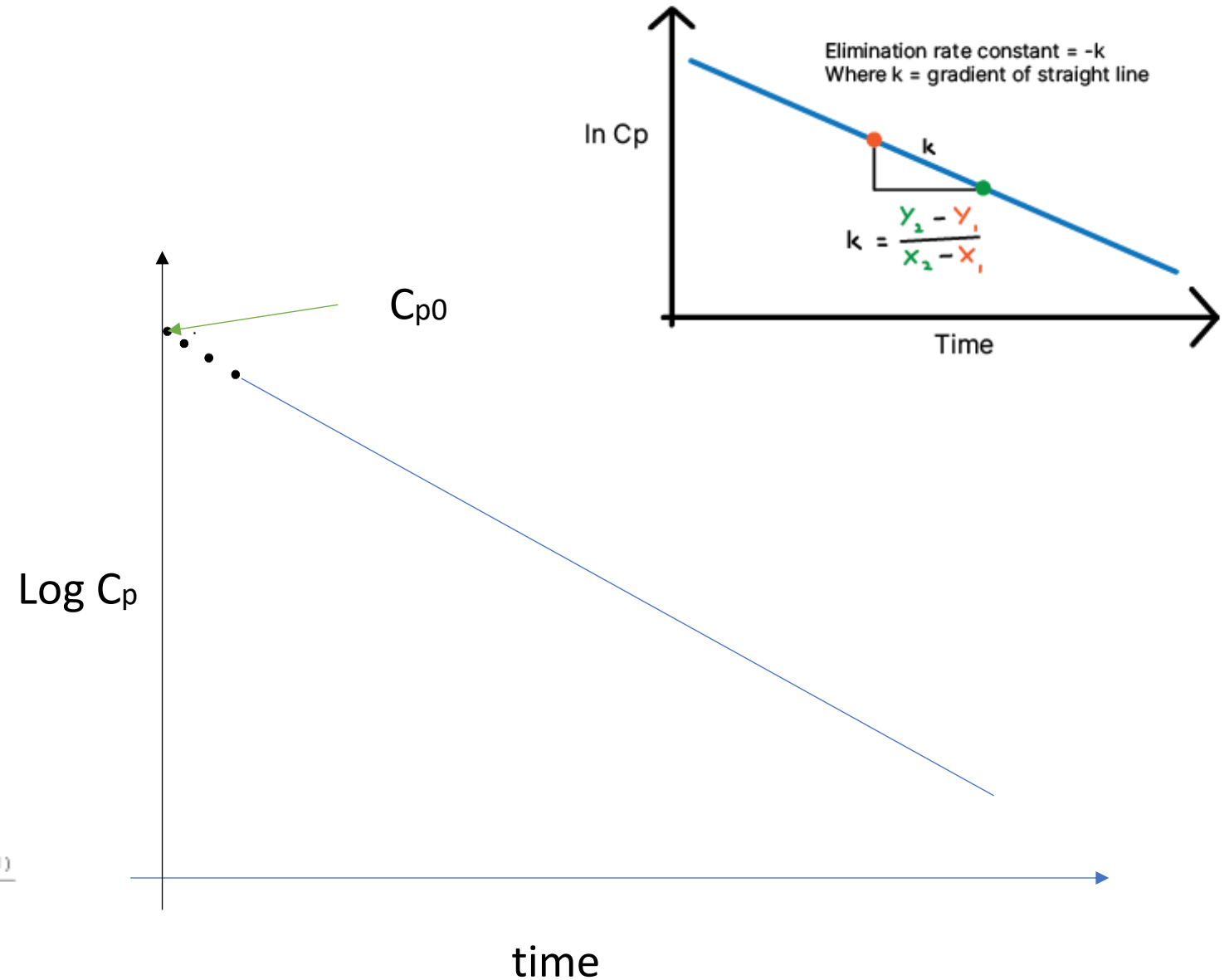
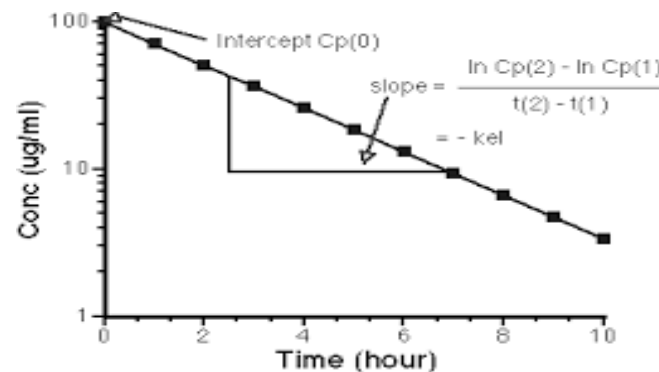
It is used for resolving a curve into its various exponential components

i.e. we use the **log** to straighten the curve

$$\text{Thus AUC} = \frac{Cp_0}{K}$$

$$K = \text{slope} * -2.303$$

$$\text{Slope} = \frac{-k}{2.303}$$



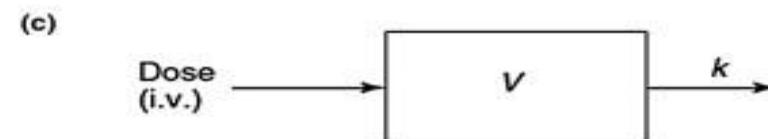
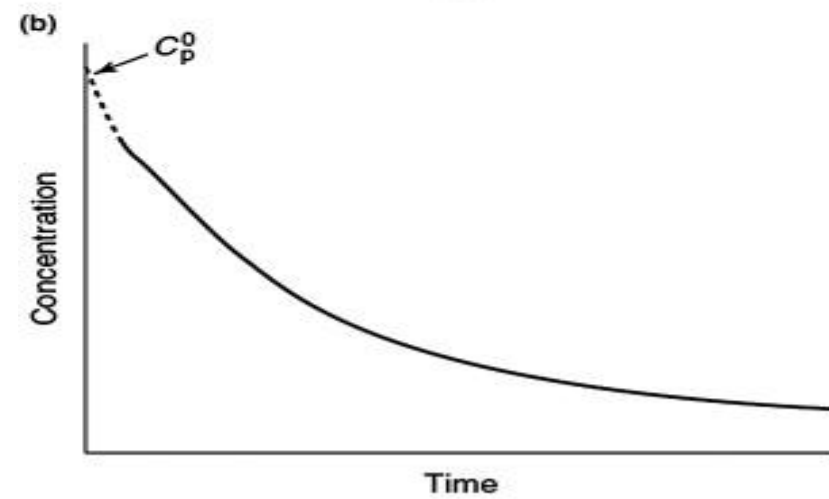
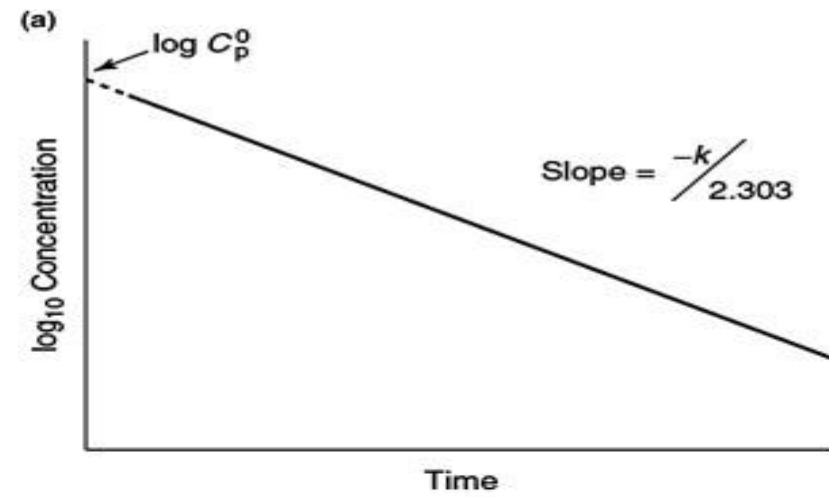
First order kinetics

$$Y = c + bX$$

$$\text{Log } C = \text{Log } C_0 \pm \frac{K}{2.303} t$$

$$\text{AUC} = \frac{C_{po}}{K}$$

$$\text{Slope} = \frac{\Delta Y}{\Delta X} = \frac{Y_2 - Y_1}{X_2 - X_1} = \frac{\text{Log } Y_2 - \text{Log } Y_1}{X_2 - X_1}$$

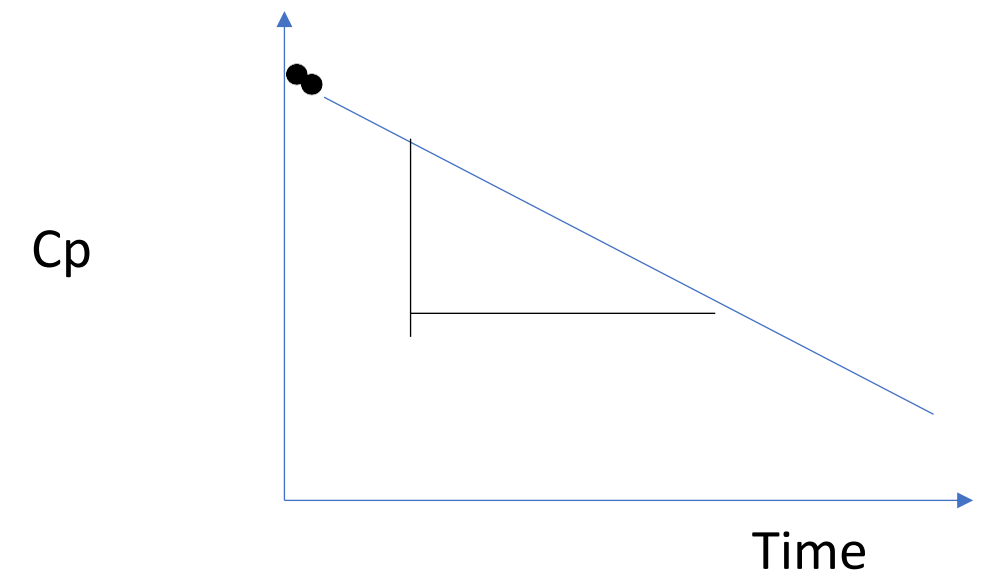


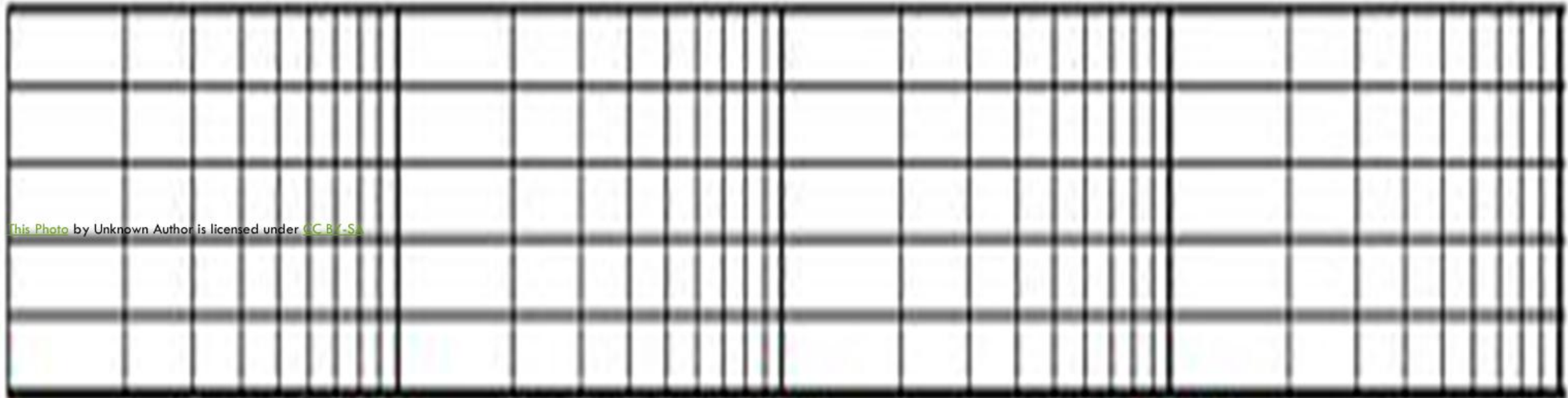
The second method: **Visual method**

By using **Semilog paper** after curve fitting for the best line, the intercept is equal to Cp_0 and to find the slope from the curve we take two points on the straight line as follow

$$\text{slope} = \frac{\log Cp_2 - \log Cp_1}{\text{time } 2 - \text{time } 1}$$

$$K = \text{slope} * -2.303$$





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1 2 3 4 5 6 7 8 9 **10** 20 30 40 50 **100** 200 300 400 500 **1000** 2000 3000 4000 5000

$$\text{AUC}_{t_0 \rightarrow t_\infty} = \int_{t_0}^{\infty} c \, dt$$

Since :

$$\log c_t = \log c_0 \pm \frac{Kt}{2.303}$$

Or:

$$\ln c = \ln c_0 - Kt$$

Then:

$$c = c_0 e^{-Kt}$$

Thus:

$$\text{AUC}_{t_0 \rightarrow t_\infty} = \int_{t_0}^{\infty} c_0 e^{-Kt} \, dt$$

The integration of this yield:

$$\text{AUC} = \frac{c_0}{-K} \left[e^{-Kt} \right]_0^{\infty}$$

$$= -\frac{c_0}{K} [0 - 1]$$

$$= \frac{c_0}{K} \text{ or } \frac{c_{po}}{K}$$

the previous equations sometimes are written as follows:

$$c_p = A e^{-\alpha t}$$

$$A = c_{po}$$

$$\text{AUC} = \frac{A}{\alpha}$$

$$\alpha = K \text{ (elimination rate constant)}$$

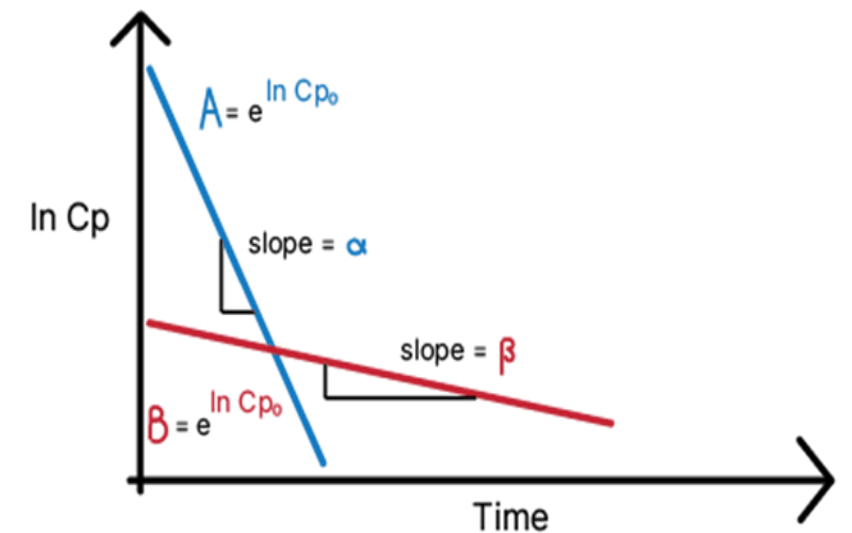
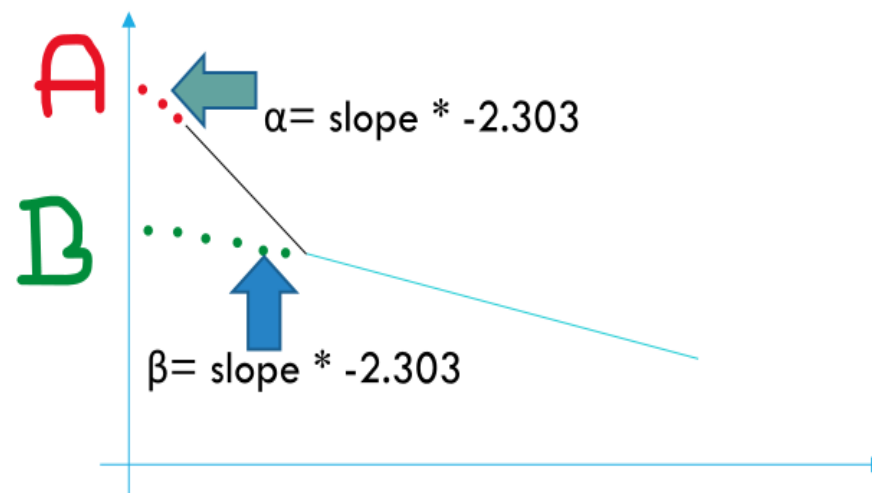
METHODS FOR ESTIMATION OF AUC FOR IV TWO COMPARTMENT MODEL

In IV two compartment model we calculate the AUC by dividing the total area into two parts and estimates the area for each one which are elimination phase and distribution phase area

The biexponential curve shown in the figure is commonly seen after the IV drug administration such curve can be described by the following eq.

$$AUC = \frac{A}{a} + \frac{B}{\beta}$$

$$A + B = C_{p0}$$



Note:

Generally, after the IV drug administration (apparent first order fast disposition rate constant, AKA distribution rate constant) is much larger than β (apparent first order slow elimination rate constant, AKA elimination rate constant)

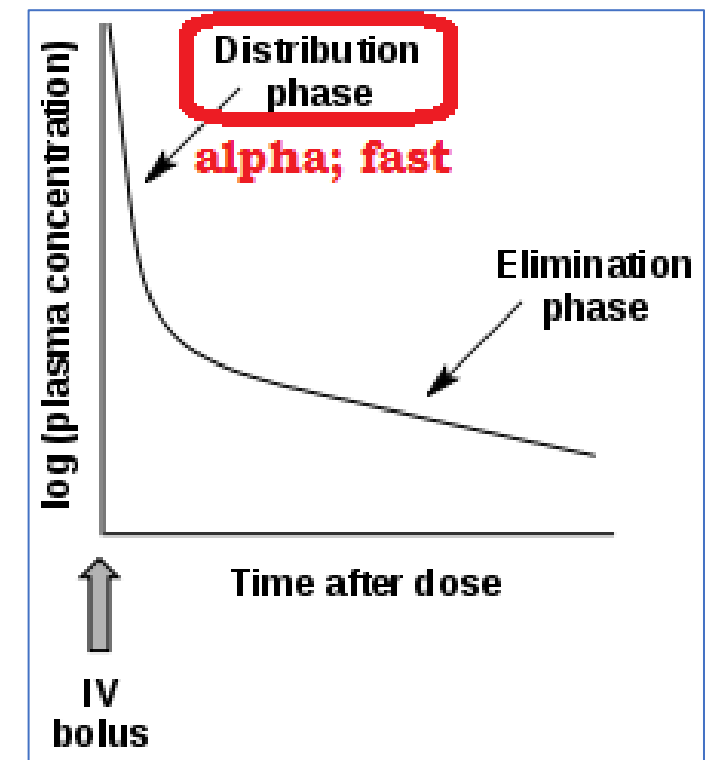
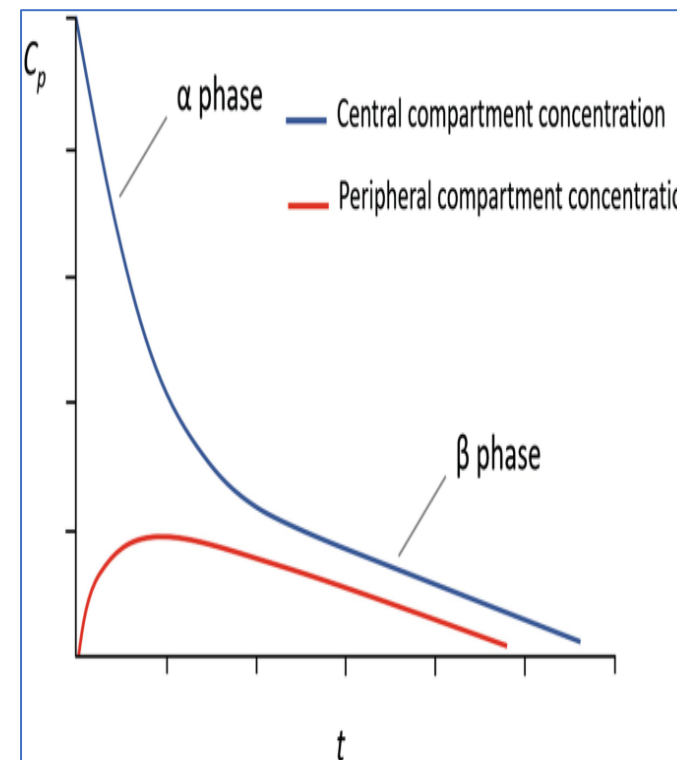
$$\alpha t_{1/2} = \frac{0.693}{K_{el}}$$

Unit of K of elimination = 1/TIME
(Time⁻¹)

$$k_{el} = \frac{-dC_p/dt}{C_p}$$

$\frac{\text{mass/volume}}{\text{time}} \div \frac{\text{mass/volume}}{\text{volume}} = \frac{1}{\text{time}}$
--

1 / hour Or Hr⁻¹



Note:

In general, in estimating AUC from time zero to time infinity and to get the best result it should be the following:

- 1- sampling early enough
- 2- sampling intervals is short
- 3- sampling for 6-8 half life



- ▶ Keep sampling for at least 6-8 $t_{1/2}$
- ▶ For example atenolol $t_{1/2} = 1$ day so keep sample for 7 days

Dose	time (day)
100	0
50	1
25	2
12.5	3
6.25	4
3.125	5
1.6	6
0.8	7



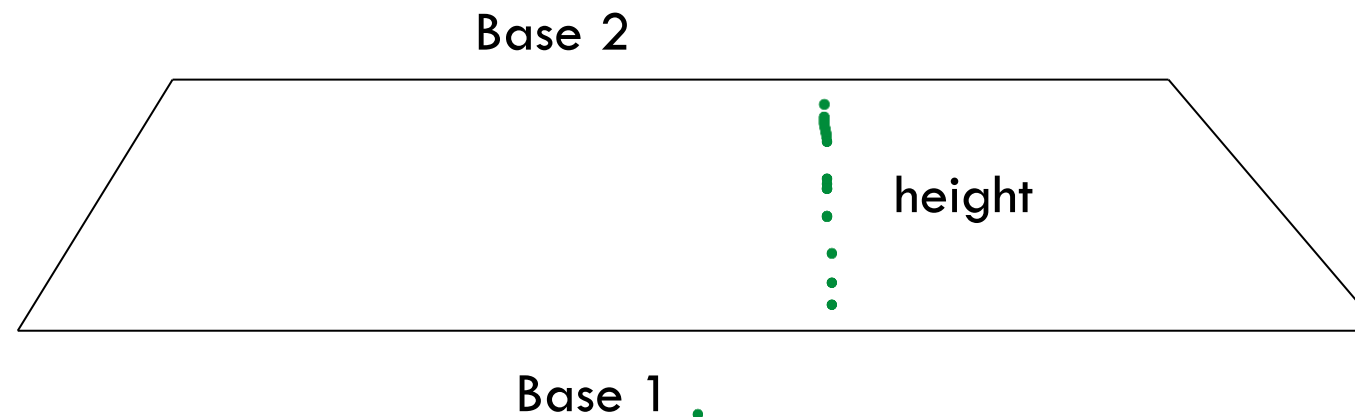
TRAPEZOIDAL METHOD

$$\text{Area of trapezoid} = \frac{(\text{base 1} + \text{base 2})}{2} \cdot \text{Height}$$

If we reverse this trapezoid, then:

Height = Time

Base = Conc.



Ln Concentration

C_{max}

Trapezoidal Method

Time

T_{max}

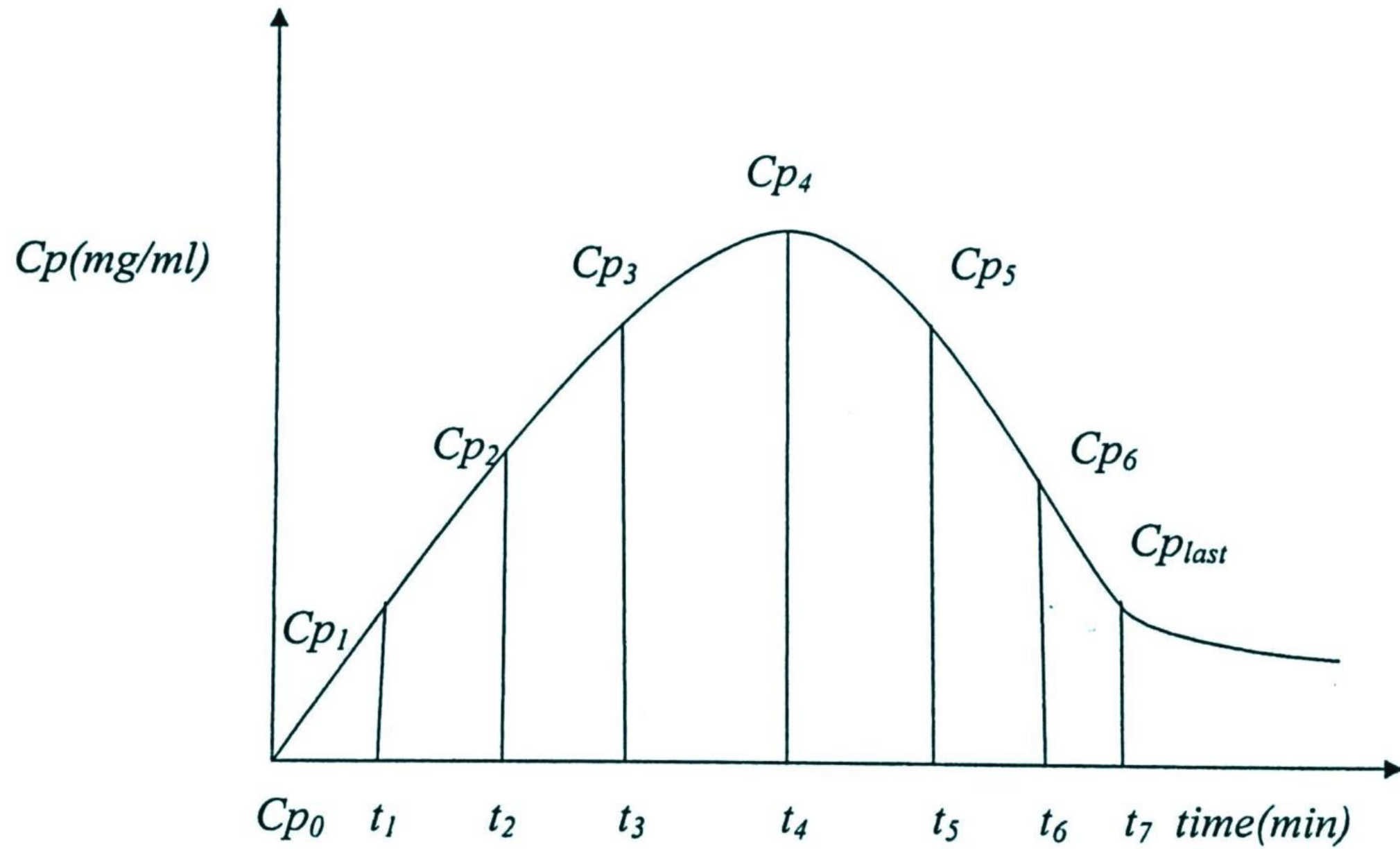


AREA OF TRAPEZOID

$$\text{Area of trapezoid} = \frac{(C_{p2} + C_{p1})}{2} \cdot (t_2 - t_1)$$

After oral administration the concentration of the drug at zero time is zero thus simply the first area is $= \frac{(C_{p2} + 0)}{2} \cdot (t_2 - 0)$

Usually, total AUC means the area under the curve from time zero to time t, therefore the area from the last sampling (concentration) to time infinity (usually called residual area) is measured as the last drug concentration divided by the elimination rate constant.



$$AUC_{(T_0 \rightarrow \infty)} = AUC_1 + AUC_2 + AUC_3 + \dots + AUC_{last}$$

If there is any fluctuation in the curve it should be calculated.

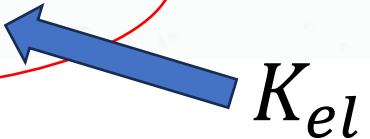
$$AUC_0 \text{ or } AUC_{extrapolated} = \frac{Cp_0 + Cp_1}{2} (t_1 - t_0) = \frac{Cp_1}{2} \times t_1$$

$$AUC_1 = \frac{Cp_1 + Cp_2}{2} (t_2 - t_1)$$

$$AUC_2 = \frac{Cp_2 + Cp_3}{2} (t_3 - t_2)$$

$$AUC_3 = \frac{Cp_3 + Cp_4}{2} (t_4 - t_3) \dots \dots \dots$$

$$AUC_{last} = \frac{Cp_{last}}{\beta}$$

 K_{el}

UNITS OF AUC

Conc. * time

Mg. hr / L

