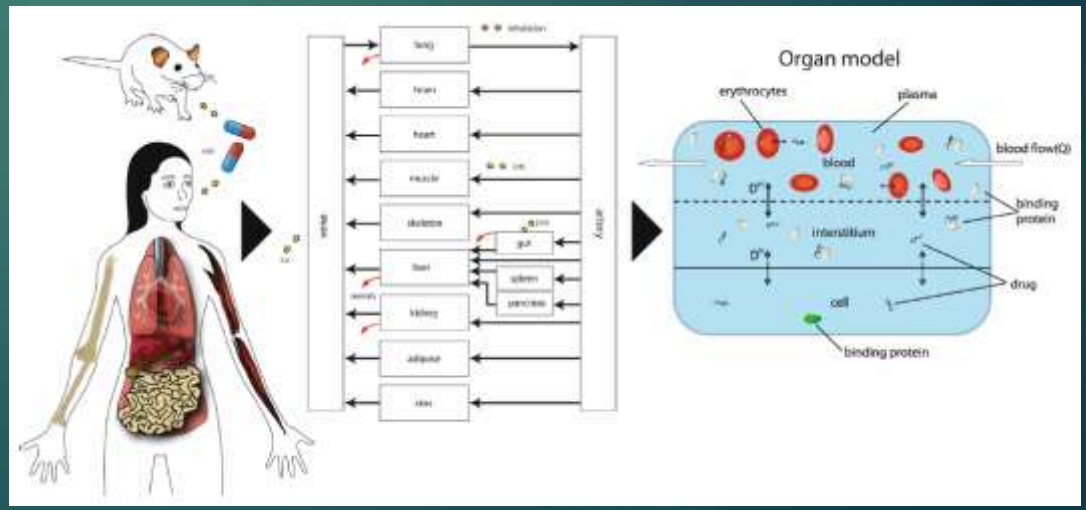
BIOAVAILABILITY BIOEQUIVALENCE AND PHARMACOKINETIC

Pharmacokinetic

It is a branch of science that examines the profiles formed in biological fluids such as plasma, urine, saliva, lymph and spinal fluid, after the administration of active substances into the organisms in their pure and dosage forms.



What are the Basic Pharmacokinetic Parameters?

- Biological half-life
- Absorption rate constant
- Elimination rate constant
- Clearance
- Distribution volume
- Average life expectancy

Bioavailability

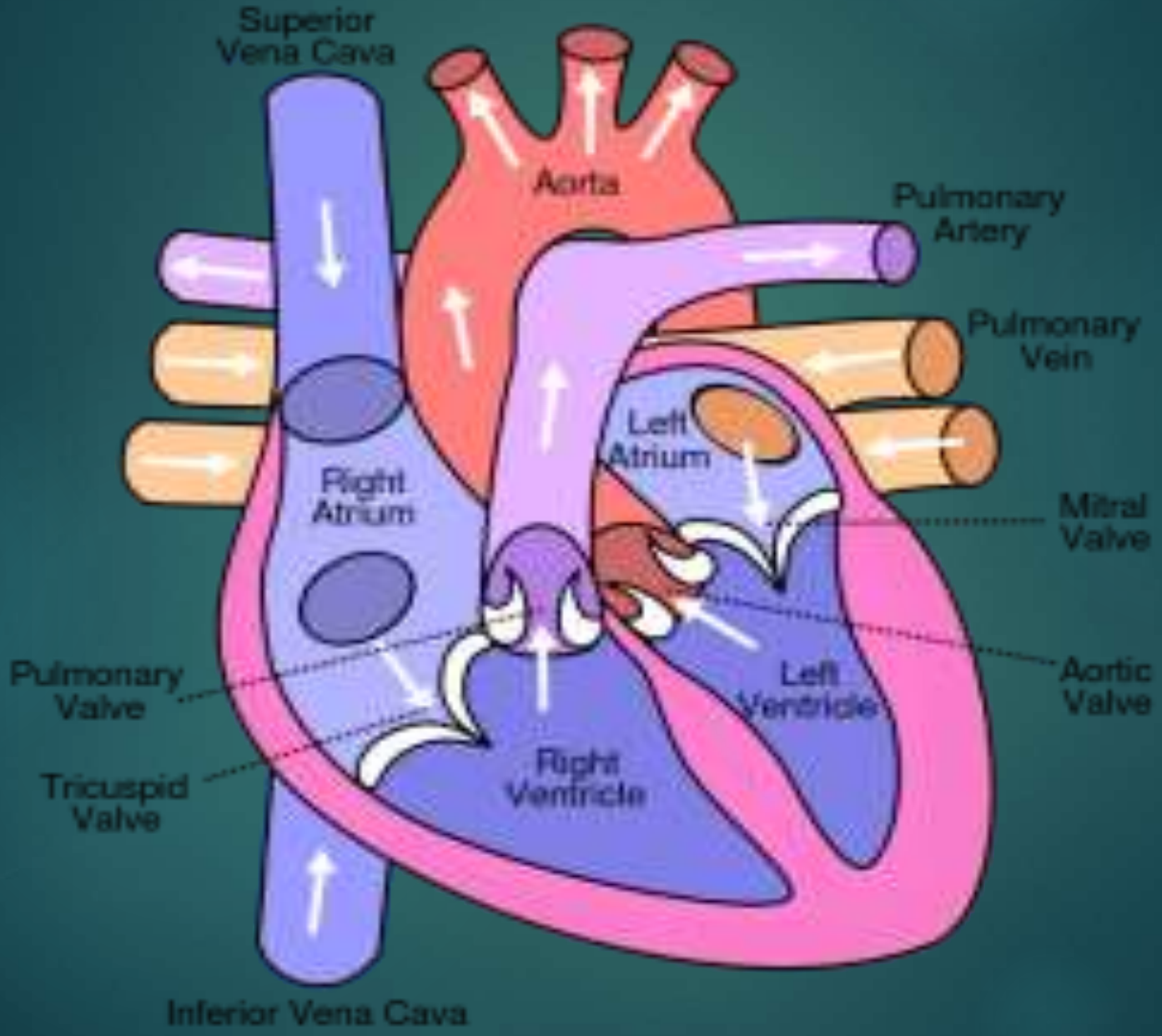
- Bioavailability is described as the passage of the active substance in the blood of the orally administered drug for pharmacokinetically and the therapeutic effect of the drug is seen in the patient for pharmacodynamically.

Absorption rate

Degree of absorption

- Bioavailability is a concrete measure of how much the body has benefited from the drug given to make a systemic effect.

- Bioavailability can be broadly defined as the rate and degree of absorption of the active substance from the pharmaceutical form of the drug. The terminology «Oral Bioavailability» is used when the drug is administered orally.


Superior Vena Cava
Aorta
Pulmonary Artery
Pulmonary Vein
Left Atrium
Right Atrium
Mitral Valve
Pulmonary Valve
Aortic Valve
Left Ventricle
Tricuspid Valve
Right Ventricle
Inferior Vena Cava

- The ratio of the amount of the drug into the systemic circulation to the dose taken through oral administration is called **systemic bioavailability**.

- **Systemic Bioavailability** → **« F »**

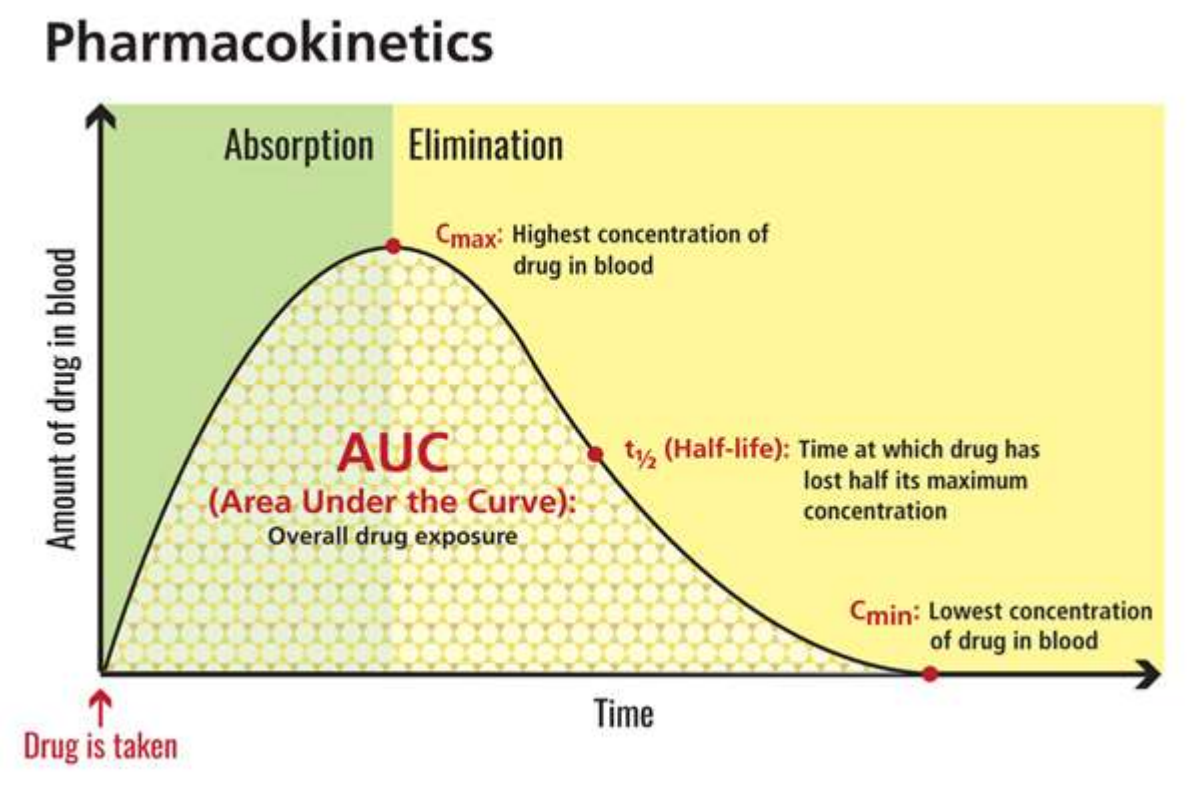
Measurement of Bioavailability

- Although the absorption rate is about 100% or less, the drugs with low systemic bioavailability are presystemic elimination (first pass elimination).

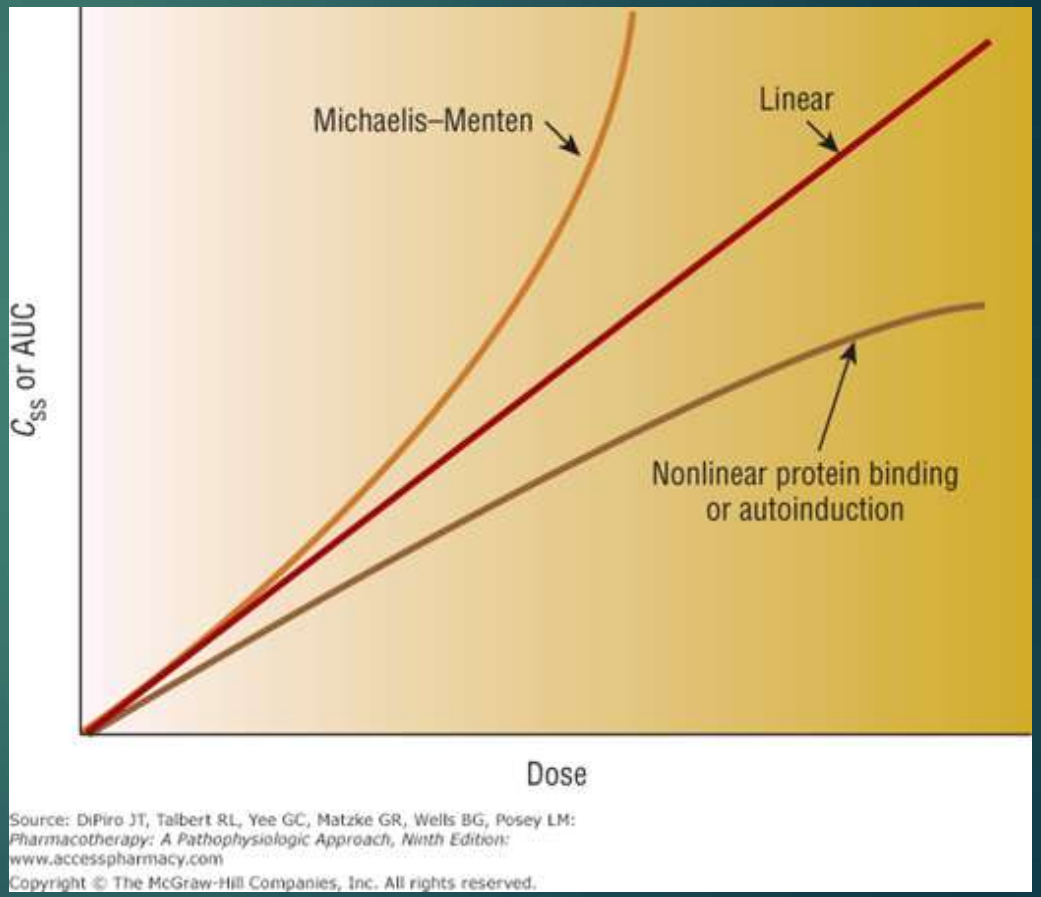
- For example, the systemic bioavailability of propranolol is 10%. → F = 0.1

- The main event in the measurement of oral bioavailability of drugs is the « plasma concentration-time curve ».
- (AUC $_{0\rightarrow\infty}$= Area Under the Curve)

$$AUC(0-\infty) = \int_0^{\infty} C(t) * dt$$



- For linear pharmacokinetics, the area under the curve (AUC) $_{0\rightarrow\infty}$ is directly proportional to the dose.
- For example, if the dose increases by 50%, the AUC increases by 50%.
- However, in non-linear pharmacokinetics, AUC is disproportional to the dose.



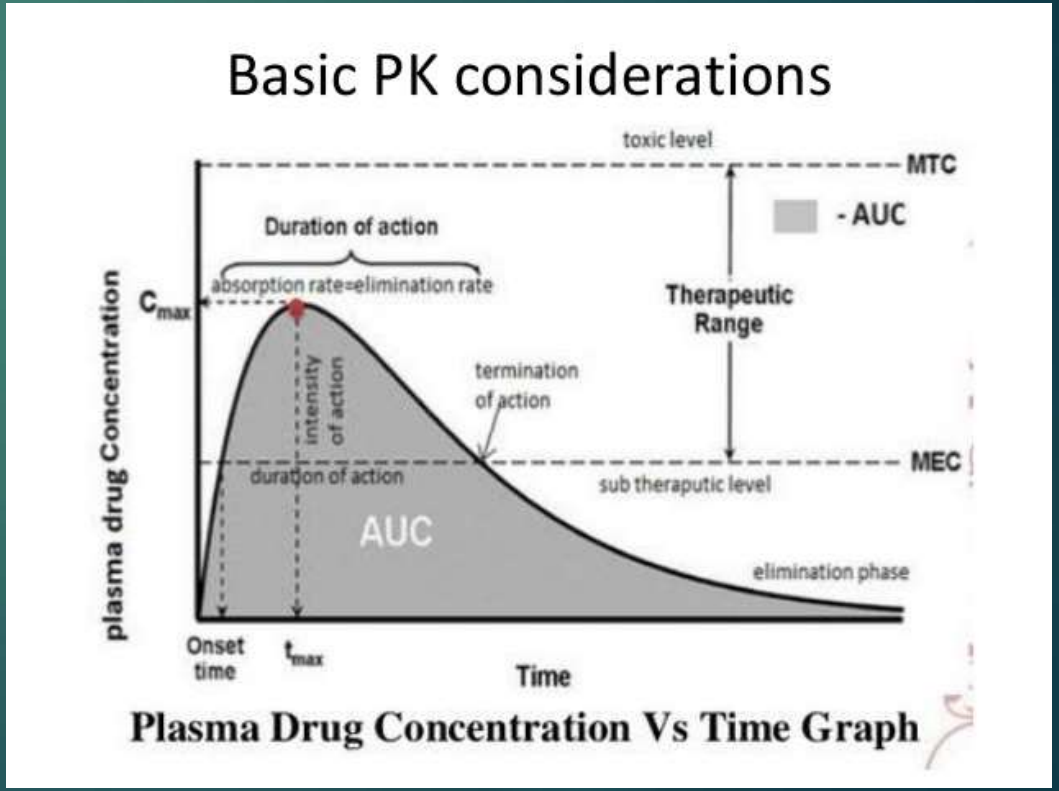
Source: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy: A Pathophysiologic Approach, Ninth Edition:* www.accesspharmacy.com

- According to this approach, a drug can be administered to a specific dose of both i.v. and oral route, the systemic bioavailability of the drug can be determined by administering the plasma concentration-time curve twice in the same subject and calculating the ratio of the $AUC_{0\rightarrow\infty}$ values to each other.

Measurement of Bioavailability

Pharmacokinetic parameters mainly studied in the measurement of bioavailability of dosage forms or different drugs containing the same active substance:

$AUC_{0\rightarrow\infty}$, C_{max} , t_{max}

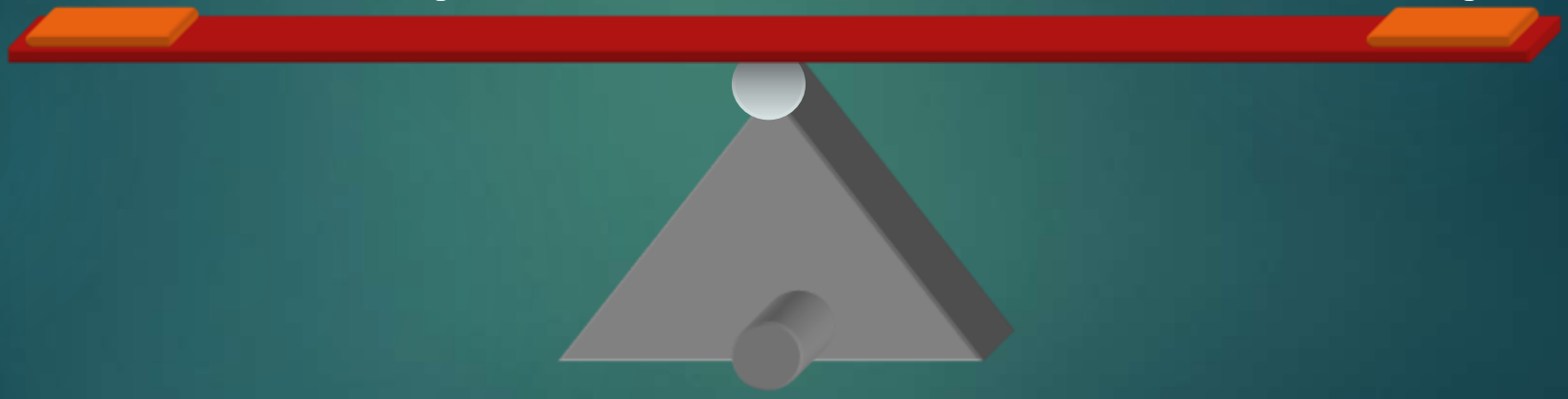


Methods Used for Measurement of Bioavailability

- Measurement of bioavailability in blood
- Measurement of bioavailability through urinary drug excretion
- Single dose given applications
- One-to-one dosing, multiple dosing, bioavailability investigations
- Measurement of bioavailability through acute pharmacological effect
- Measurement of the bioavailability of prodrugs

Absolute Bioavailability

Rolative Bioavailability



«Absolute bioavailability» refers to amount of the drug available to the body or system. This is measured as a ratio between the AUC after intravenous administration and AUC oral administration. It should be a figure less than 1 since it is assumed that 100% of the drug is available to the body after IV administration. The IV dose is assumed to be 100% bioavailable … since you are injecting the drug directly into the systemic circulation.

$$F = \frac{AUC_{oral}}{AUC_{IV}}$$

Absolute bioavailability determines how much of the active substance is absorbed from the dosage form administered by the way the absorption process takes place.

“Relative bioavailability” is the amount of drug from a formulation that reaches the systemic circulation relative to a different formulation (non-IV) such as oral solution, reference formulation, etc. Relative bioavailability is commonly used when an IV formulation does not exist or cannot be made.

$$F_{rel} = \frac{AUC_{formulation_1}}{AUC_{formulation_2}}$$

Why is bioavailability determined?

- To determine the absolute bioavailability of a drug
- To determine whether the bioavailability parameters of the drug are proportional to the dose
- To determine the extent of intra-subject and inter-subject change with single-dose administration
- To investigate the effect of nutrients and combined drug therapy on bioavailability
- Formulation changes
- To prove whether the generic drug is equivalent to an innovative product

Bioequivalence

This term defines that the rate and the amount (bioavailability) of the active substance contents of the pharmaceutical equivalent or the pharmaceutical alternative products are the same.

Concepts of Equivalence

- Pharmaceutical Equivalence
- Therapeutic Equivalence
- Chemical Equivalence
- Pharmaceutical Alternative
- Therapeutic Alternative

Pharmaceutical Equivalence:

To be considered pharmaceutical equivalents, 2 drugs must contain the same active ingredient(s), have the same dosage form and route of administration, and have identical strength or concentration. Pharmaceutically equivalent drugs may differ, however, in shape, scoring configuration, release mechanisms, packaging, excipients (including colors, flavors, preservatives), expiration time, and labeling (within certain limits).

Chemical Equivalence:

This concept indicates that two or more forms of drugs contain the same active substance in the amounts specified in the labels (within certain limits of the deviation).

Pharmaceutical Alternatives:

Drugs are considered to be pharmaceutical alternatives if they contain the same therapeutic moiety but are different salts, esters, or complexes of that moiety (eg, tetracycline hydrochloride vs tetracycline phosphate complex); or are different dosage forms or strengths (eg, quinidine sulfate tablets vs quinidine sulfate capsules).

Therapeutic Equivalence:

Therapeutically equivalent drugs have the same pharmacokinetic and pharmacodynamic properties.

They have been proven bioequivalent and the FDA believes they can be expected to have the same clinical effect and adverse-events profile.

Two drugs are considered therapeutic equivalent if they:

- Are approved as safe and effective

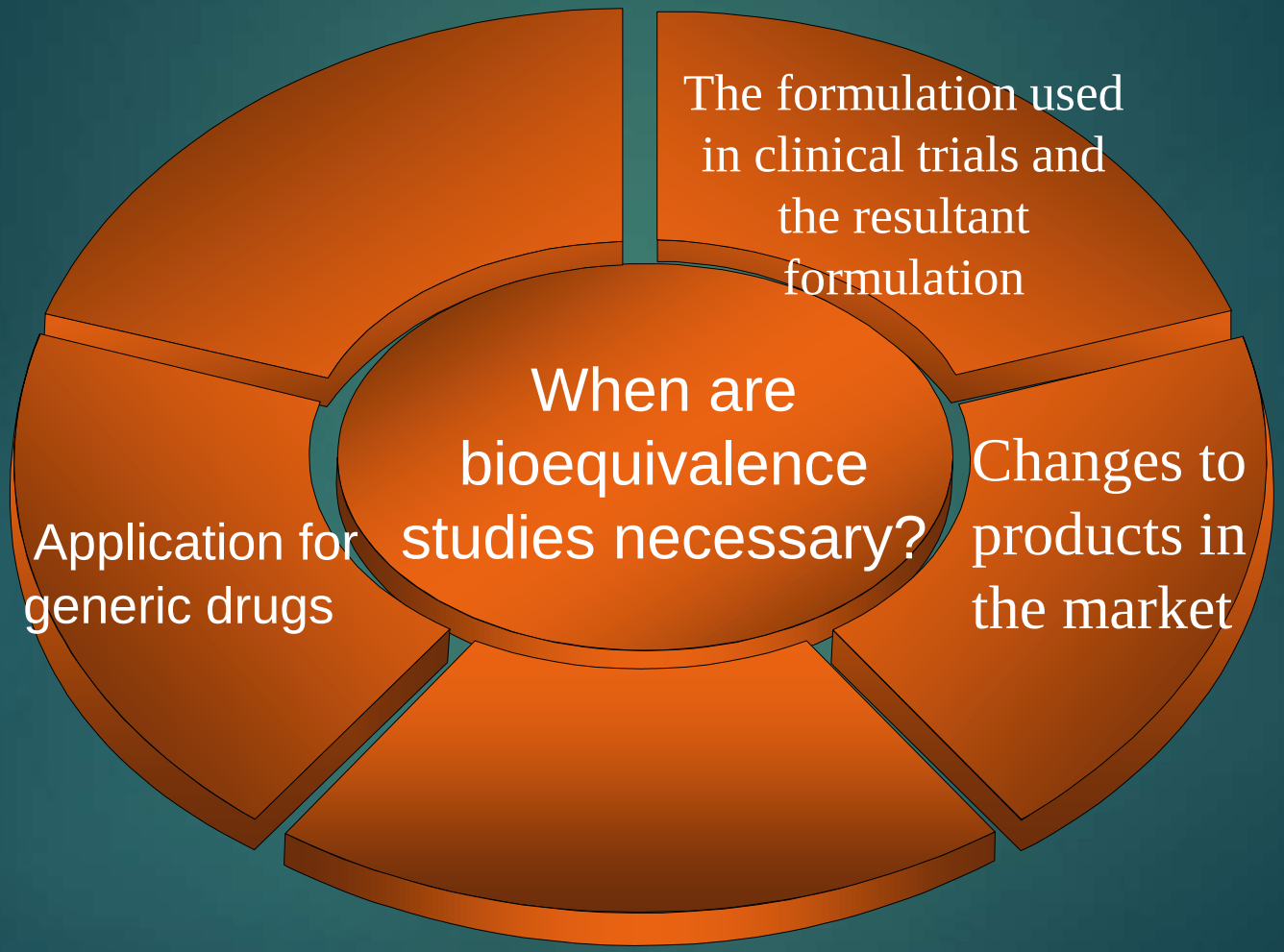
- Are pharmaceutical equivalents (for example, they contain identical amounts of the same active drug ingredient, are in the same dosage form, and have the same route of administration)

- Meet compendial or other applicable standards in terms of strength, quality, purity, and identity

Therapeutic Alternatives:

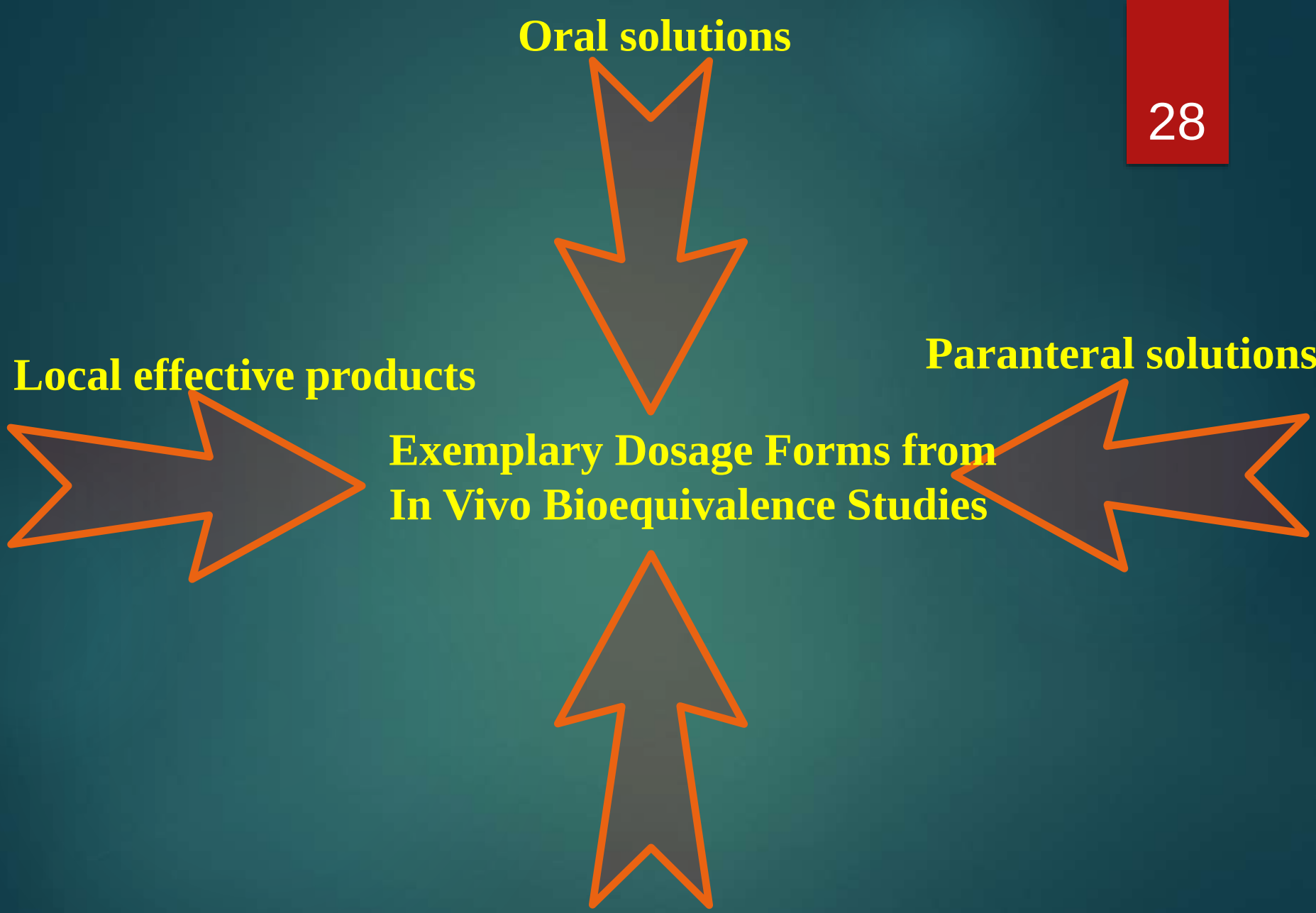
Therapeutic alternatives are drugs that may have chemically different contents but are purported to have the same effect as other drugs for treating a condition.

For example; acetylsalicylic acid and ibuprofen.


When are bioequivalence studies necessary?
The formulation used in clinical trials and the resultant formulation
Changes to products in the market
Application for generic drugs

When is a bioequivalence study required?

- In case of chemical structure of excipients
- In case of change in the contribution rates of the excipients used (% of the amounts in the formula)
- In case of change of production method
- In case of changes in active substance
- In case of changing of the production center of the dosage form
- In the case of the use of a new pharmaceutical form without any change in the dosage regimen


Oral solutions
Local effective products
Paranteral solutions
Exemplary Dosage Forms from
In Vivo Bioequivalence Studies
Inhalation gases

Demonstration of Bioequivalence of Products

- Pharmacokinetic study
- Pharmacodynamic study
- Clinical study
- In vitro dissolution rate study

- The fate of a drug entering the organism depends on some kinetic events.

- Studies investigating these kinetic events are called as «pharmacokinetic modeling studies».

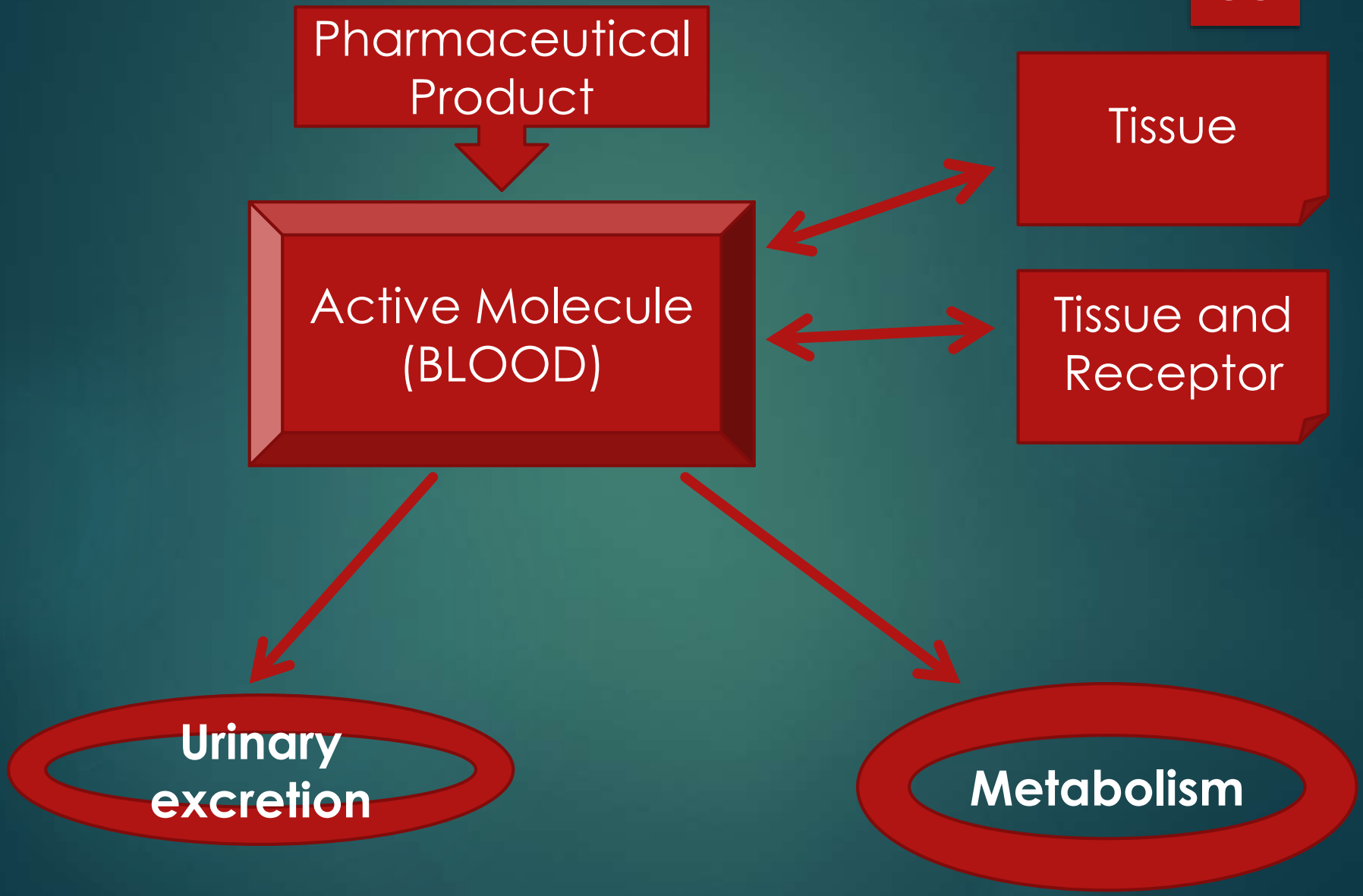
Pharmacokinetic Modeling

- To describe the behavior of active substances through mathematical equations when they are given to the organism is called «Modelling».
- As the body is considered to be one piece and it is very difficult to examine the ADME stages in this way, the body is divided into independent sections called «Compartment».
- That is, if the drug is present in detectable concentrations in different parts of the body, each of these regions is called «Compartment».

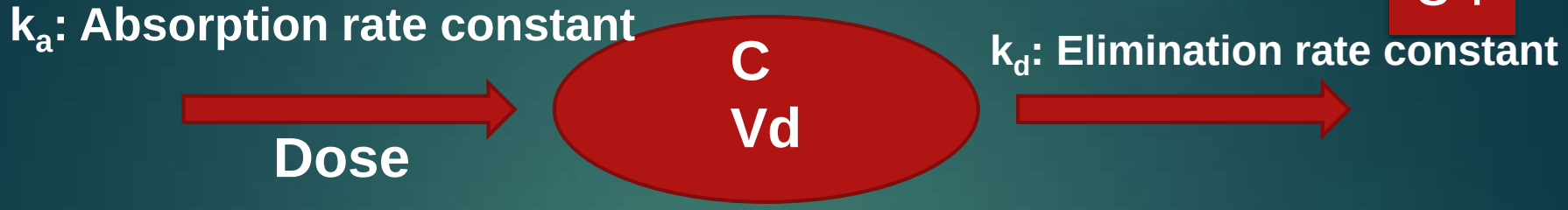
Compartment Models

Active ingredient;

- **With IV injection**
- **With IV infusion**
- **With absorption routes (oral, IM, rectal, vaginal, transdermal, nasal, etc.)**


Pharmaceutical Product
Active Molecule (BLOOD)
Tissue
Tissue and Receptor
Urinary excretion
Metabolism

One Compartment Model



- The entry and exit of the drug into the compartment is usually with **first order kinetics**.
- Drugs absorbed by **passive diffusion transport mechanism** exhibit first-order kinetics.
- There is no metabolism product and 100% excretion from the kidneys.
- The active substance can be examined in blood (plasma / serum) and urine.

- The one compartment model is the simplest model.
- When the active molecules conform to this system are given into the body, the organism exhibits a single compartmental behavior.
- The plasma concentration of the active substance represents the concentration of the compartment.
- The volume of the compartment is the **distribution volume of the active substance (Vd),** which is an important pharmacokinetic parameter.

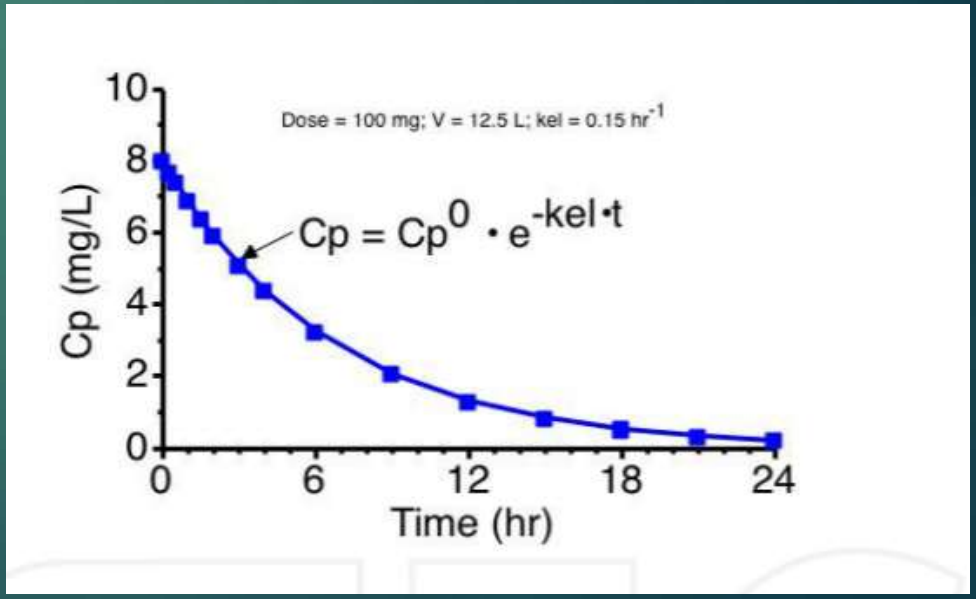
One Compartman Model – IV Injection

In this model, the body acts like a single, uniform unit in which the drug can enter or leave the body easily.

$C_0 \times Vd = Doz$

- **First Order Reaction**

$\ln C = \ln C_0 - k_{el} \cdot t$



Linear Plot of Cp versus Time for a One-Compartment IV Bolus

Apparent Volume of Distribution (Vd) Calculation

$$C_0 = D / Vd$$

C_0= Initial concentration
D = Dose
Vd= Apparent volume of distribution

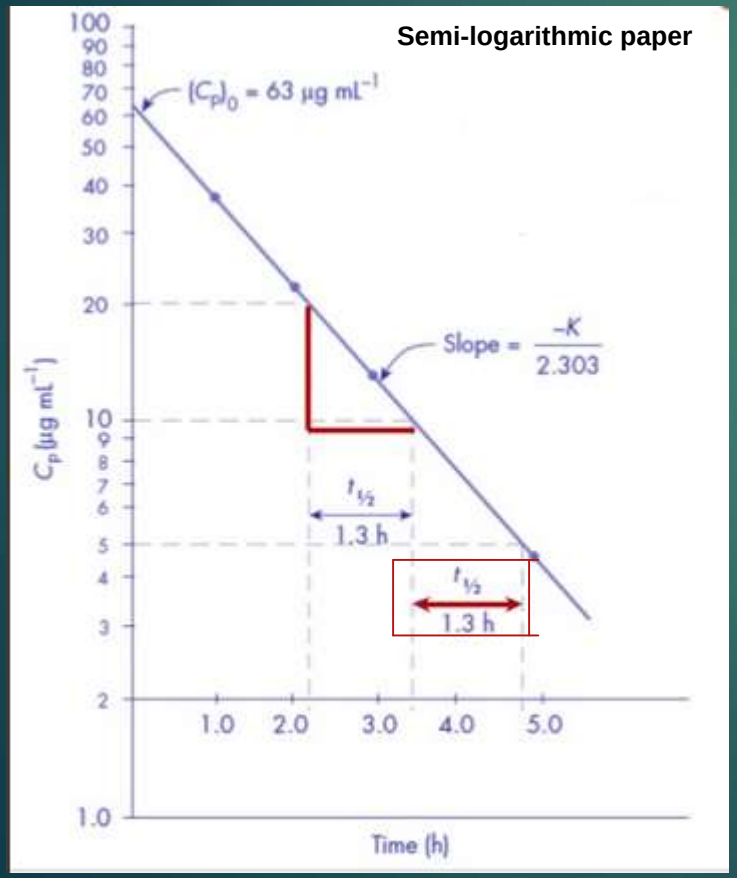
Half Time ($t_{1/2}$) and also Elimination rate constant (K)

$$-0.693 = -Kt_{1/2}$$

$$K = 0.693/t_{1/2}$$

Example 1

The blood concentration-time graph of the drug administered intravenously 600 mg is given below. Calculate the elimination rate constant of the drug and also the dose after 5 hours.



$k = 0{,}693 / t_{1/2}$

$k = 0{,}693 / 1{,}3 = 0{,}533\ hour^{-1}$

$\ln C = \ln C_0 - k.t$

$\ln C = \ln 600 - 0{,}533 \cdot 5$

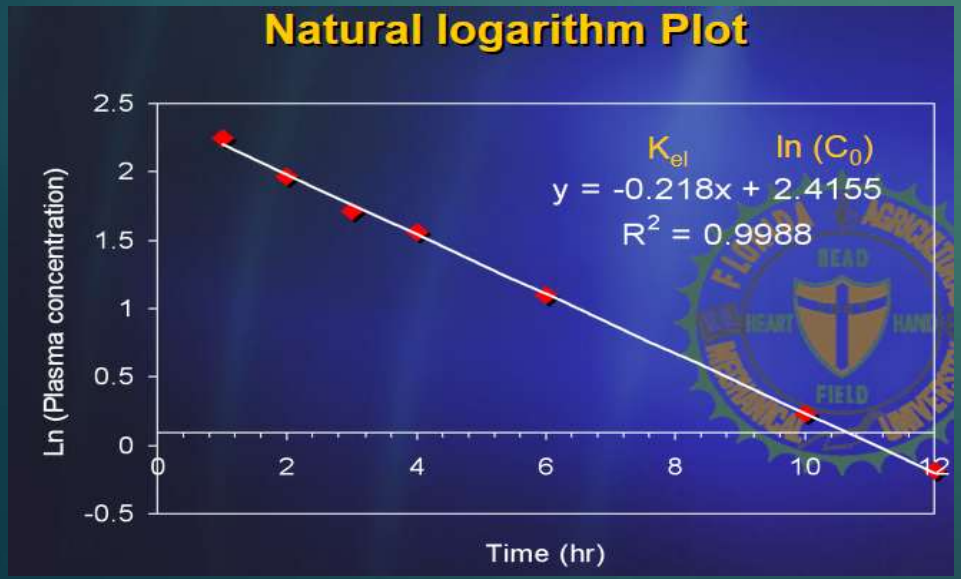
$\ln C = 6.40 - 2.67 = 3.73$

$C = 41.68\ mg$

Example 2

- IV bolus administration
- Dose = 500 mg
- Drug has a linear disposition

Time (hr)	Plasma Conc. (mg/L)	ln (Plasma Conc.)
1	9.46	2.25
2	7.15	1.97
3	5.56	1.71
4	4.74	1.56
6	3.01	1.10
10	1.26	0.23
12	0.83	-0.19



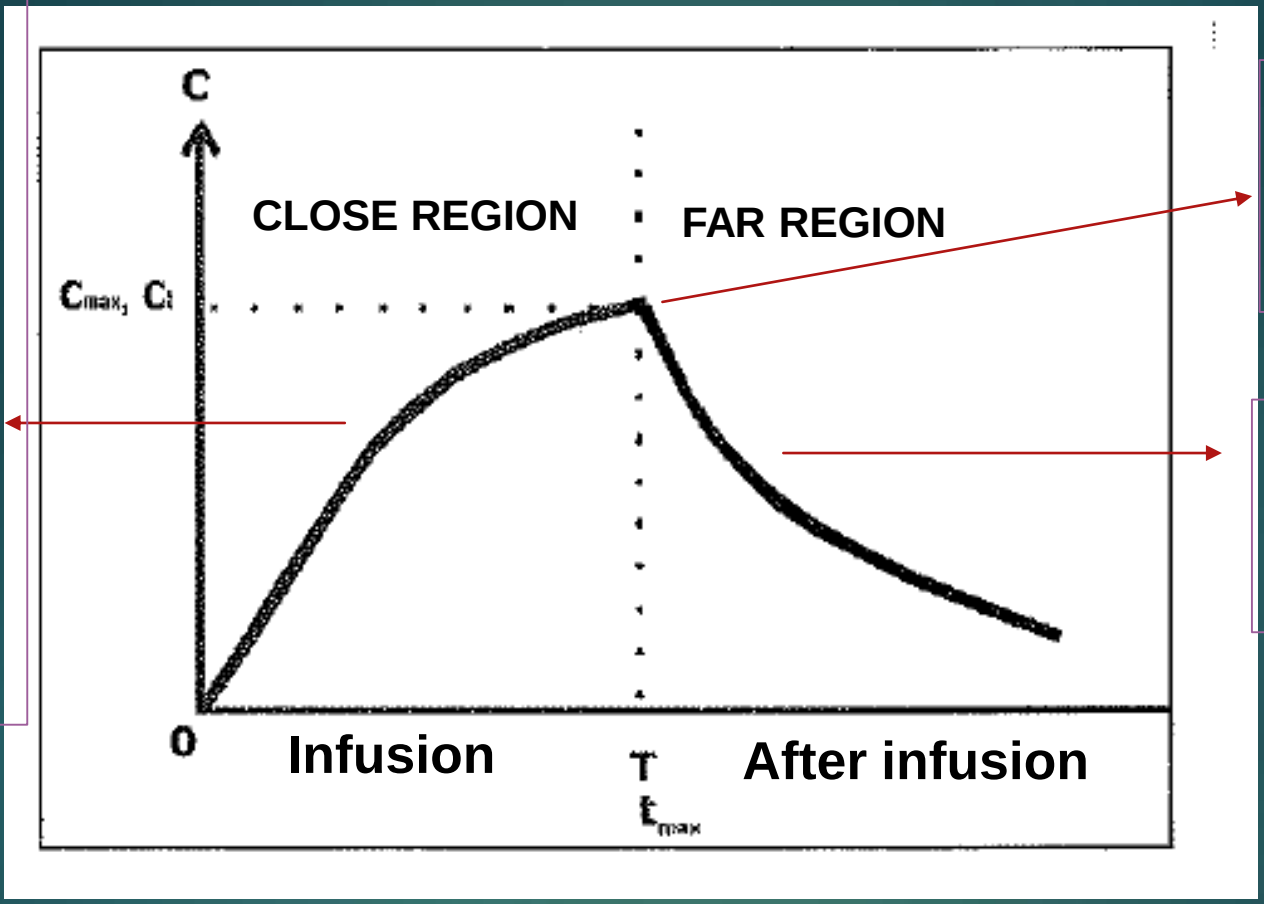
$t_{1/2} = 0.693 / K_{el} = 3.172$ hours

One Compartment Model – IV Infusion

- Drugs administered by constant IV infusion show a zero-order input process, during which the drug is introduced into the blood stream while the elimination process for most drugs is first-order. The rate of input minus the rate of output represents the change in the amount of drug in the body at any given time.

IV Infusion Plasma Profile

Zero-order input process - the drug is introduced into the blood stream

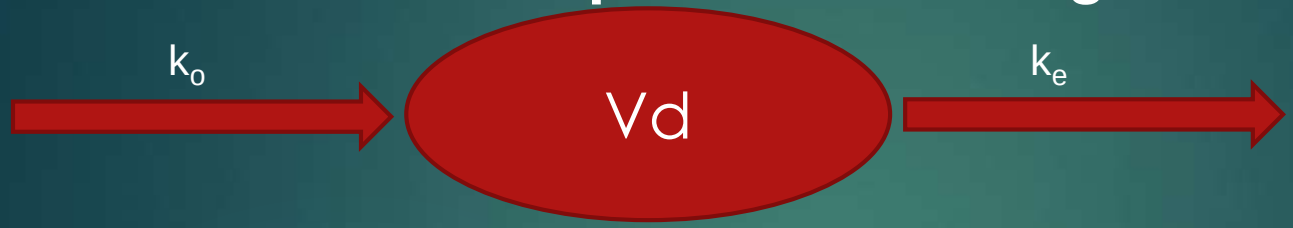


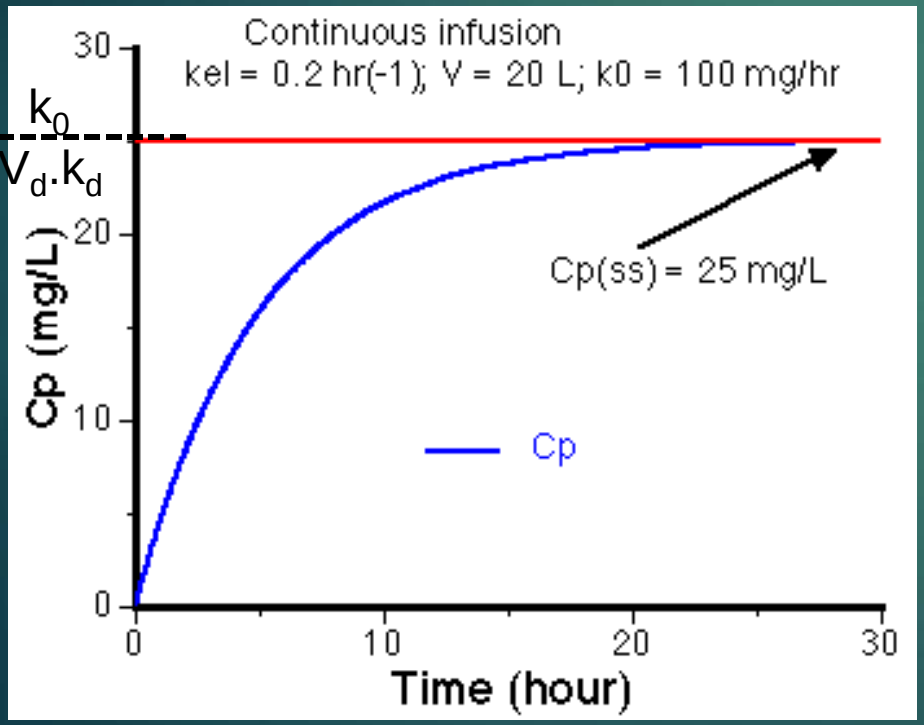
The moment that the infusion stops

First order – elimination process

- There are both drug entry and elimination in the close region.
- In the far region, there is only an elimination process.

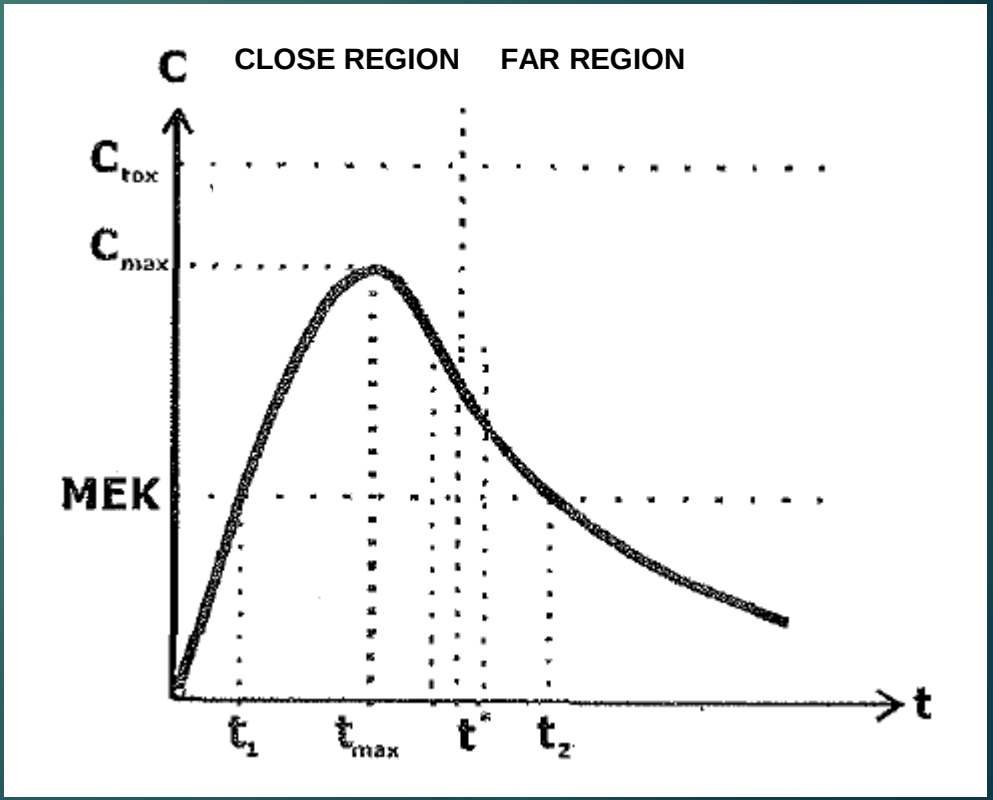
In one-compartment IV infusion model, the entry of the drug into the body is carried out with zero-degree kinetics and the output with first-degree kinetics.



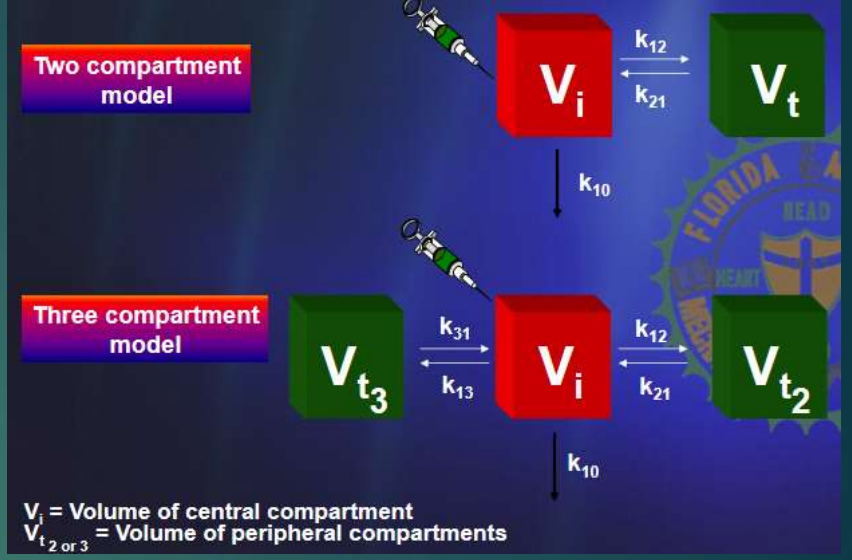


One Compartment Model – Oral Absorption (or IM)

- There is an absorption in the gastrointestinal tract. The active molecule enters the bloodstream at an increasing rate.
- As with the intravenous infusion, there is no constant speed.



Two Compartment Model



- From blood to tissue :

BLOOD → Central Compartment

TISSUE → Second Compartment

Two Compartment Distribution

For drugs in general;

- One compartment distribution,

- Two compartment distribution, or

- Multi-compartment distribution can be used. However, sometimes the drug goes directly to the liver and breaks down into its metabolites. In such a case, one more mention of the rate constant expressing the metabolism of the drug is mentioned. This is called the «metabolism rate constant».

All of these speeds are constant and are considered invariant due to individual differences. In order to determine the behavior of drugs in the body and these rate constants, a method called Method of Residuals (Stripping method, Peeling method, Feathering method) is used.

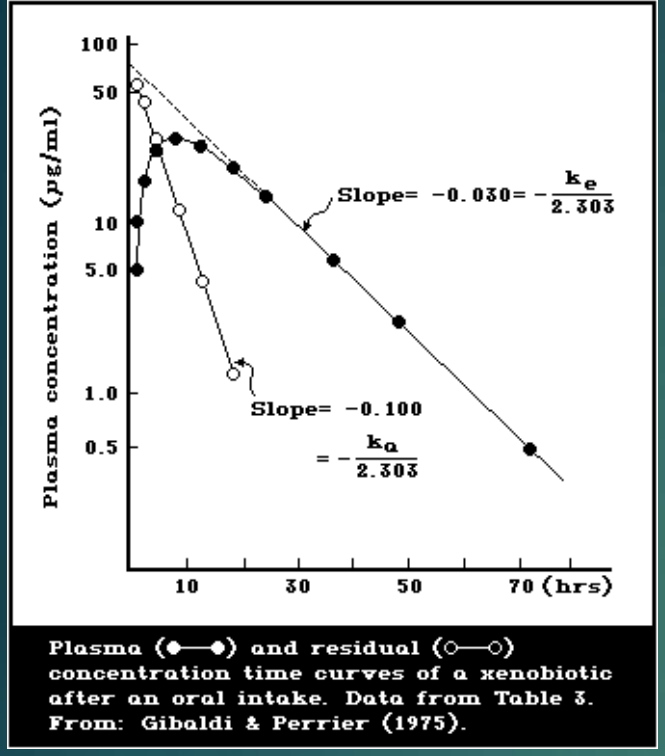
- In this method, blood concentrations are measured at different times after administration of the drug and there is a multidimensional equation that best describes the blood data obtained by linear regression analyzes.
- Each constant in this equation expresses the speed of a phase that the drug is in the body. For example;

-Absorption rate,

-Elimination rate, ….

- Once the equation describing the behavior of the active substance has been found, the blood concentration in any time period can be estimated from the patient without taking a blood sample.

Method of Residuals



Plasma (●—●) and residual (○—○) concentration time curves of a xenobiotic after an oral intake. Data from Table 3. From: Gibaldi & Perrier (1975).

Table 3. Plasma concentration-time data and calculated residual concentrations following a single oral administration of a xenobiotic (one-compartment model)

Time (h)	Plasma concentration (µg/ml)	Extrapolated concentration[a] (µg/ml)	Residual concentration[b] (µg/ml)
0.5	5.36	69.0	63.64
1	9.95	66.5	56.55
2	17.18	62.5	45.32
4	25.78	54.0	28.22
8	29.78	41.2	11.42
12	26.63	31.2	4.57
18	19.40	20.7	1.30
24	13.26		
36	5.88		
48	2.56		
72	0.49		

[a] Obtained from the extrapolated straight line (----) in Fig. 7.

[b] Calculated as the difference beteween the extrapolated line and the corresponding plasma concentrations.

1) The linear regression equation of the last 3, 4 or 5 points in the graph where the absorption coefficient is the minimum is obtained (the coefficient of determination (r^2) is greatest)

2) The values are extrapolated towards the y axis and the equation for the elimination rate constant is calculated.

3) Residual concentration is calculated from the difference between the initial plasma concentration and the extrapolated concentration in absolute value.

4) Residual concentration values are extrapolated towards the y axis and the equation for the absorption rate constant is calculated.