Biopharmaceutics

4th Stage

College of Pharmacy

Lecture 5: Bioavailability and Bioequivalence

By : Dr. Nizar Awish Jassem

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Bioavailability and Bioequivalence

- **Bioavailability (BA)** is the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action.
- For drugs intended to produce systemic effects, bioavailability is commonly evaluated by determining how much unchanged drug reaches the systemic circulation and how quickly it gets there.
- Bioavailability has **two** principal components:

  A. Extent of bioavailability
  - The extent refers to the amount of drug that reaches the systemic circulation.
  - It is commonly assessed using the **area under the plasma drug concentration–time curve (AUC)**.

  B. Rate of bioavailability
  - The rate describes how quickly the drug becomes available in the systemic circulation.
  - It is commonly assessed using:
    - Maximum plasma drug concentration (C_{max}).
    - Time required to reach maximum plasma concentration (T_{max}).

Definition of Bioequivalence

- **Bioequivalence (BE)** is the absence of a **significant** difference in the rate and extent to which the active ingredient or active moiety becomes available at the site of drug action when **two** pharmaceutical products are administered at the same molar dose under similar conditions in an appropriately designed study.
- Two products are usually designated as:
  - **Test product:** The formulation being evaluated, often a generic drug product.
  - **Reference product:** The established comparator, usually the approved reference-listed or innovator product.

Example

- A pharmaceutical company develops a generic tablet containing 500 mg of a particular antibiotic.
- The reference brand-name tablet also contains 500 mg of the same active ingredient.
- The company must demonstrate that the generic product has sufficiently similar in vivo performance to the reference product according to the applicable regulatory requirements.
- If the products meet the required criteria, bioequivalence may be established.

Purposes of Bioavailability and Bioequivalence Studies

- Bioavailability and bioequivalence studies are important tools in pharmaceutical development, quality assurance, and regulatory decision-making.
- Their main purposes are :

1. To evaluate drug absorption

- Bioavailability studies determine the rate and extent of drug availability following administration of a pharmaceutical product.

2. To compare different formulations

- They help determine whether changes in formulation, excipients, or manufacturing methods influence drug absorption.

3. To support the development of new drugs

- They establish a link between the formulation used in clinical studies and the proposed commercial formulation.

4. To support generic drug approval

- Bioequivalence studies provide evidence that a generic product performs sufficiently similarly to its reference product.

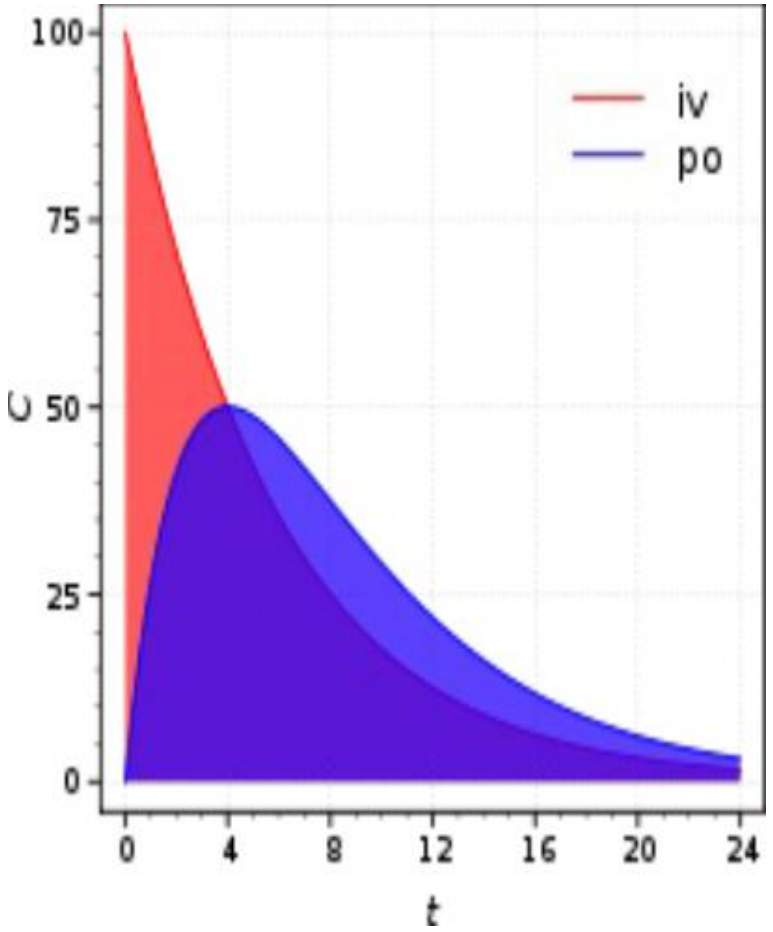
5. To evaluate modified-release formulations

- A modified-release formulation may produce a different concentration–time profile from an immediate-release product. Comparative studies help characterize these differences.

Types of Bioavailability

1- Absolute Bioavailability

- **Absolute bioavailability (F)** is the fraction of an administered **dose** that reaches the systemic circulation unchanged following administration by a particular route, compared with intravenous administration of the same drug.
- **Intravenous administration** is used as the reference because the entire administered dose enters the systemic circulation directly. Therefore, its absolute bioavailability is defined as 100%.
- For an **orally administered drug**, absolute bioavailability **may be less than 100%** because of **incomplete absorption, degradation in the gastrointestinal tract, or presystemic metabolism**.
- Absolute bioavailability compares systemic exposure after an extravascular dose with systemic exposure after an intravenous dose, correcting for differences in the administered doses.



Formula for Absolute Bioavailability

- Absolute bioavailability is calculated using the dose-corrected AUC values obtained after non-intravenous and intravenous administration.

$$F = \frac{AUC_{\text{non-IV}} \times D_{\text{IV}}}{AUC_{\text{IV}} \times D_{\text{non-IV}}}$$

$$F = \frac{AUC_{\text{oral}} \times D_{\text{IV}}}{AUC_{\text{IV}} \times D_{\text{oral}}}$$

$$F(\%) = \frac{AUC_{\text{oral}} \times D_{\text{IV}}}{AUC_{\text{IV}} \times D_{\text{oral}}} \times 100$$

F: Absolute bioavailability.

AUC_{oral}: Area under the plasma concentration–time curve after oral administration.

AUC_{IV}: Area under the plasma concentration–time curve after intravenous administration.

D_{oral}: Oral dose administered.

D_{IV}: Intravenous dose administered.

Example Calculation of absolute bioavailability

- A drug is administered to a volunteer under two condition

Parameter	Oral tablet	IV injection
Dose	200 mg	50 mg
AUC	80 mg·h/L	40 mg·h/L

Calculate the absolute bioavailability of the oral tablet.

$$F = \frac{AUC_{\text{oral}} \times D_{\text{IV}}}{AUC_{\text{IV}} \times D_{\text{oral}}}$$

$$F = \frac{80 \times 50}{40 \times 200}$$

$$F(\%) = 0.50 \times 100$$

$$\boxed{F = 50\%}$$

Factors Responsible for Low Absolute Bioavailability

- Absolute bioavailability can be reduced by several factors.

1. Incomplete absorption

- Some drugs are poorly absorbed because of low membrane permeability, inadequate dissolution, or other physiological and physicochemical limitations.

2. Poor aqueous solubility

- A drug must generally dissolve before it can be absorbed from the gastrointestinal tract.

3. Chemical instability

- Some drugs degrade in the gastrointestinal environment before absorption. For example, an acid-sensitive drug may be degraded in the stomach unless an appropriate formulation protects it.

4. First-pass metabolism

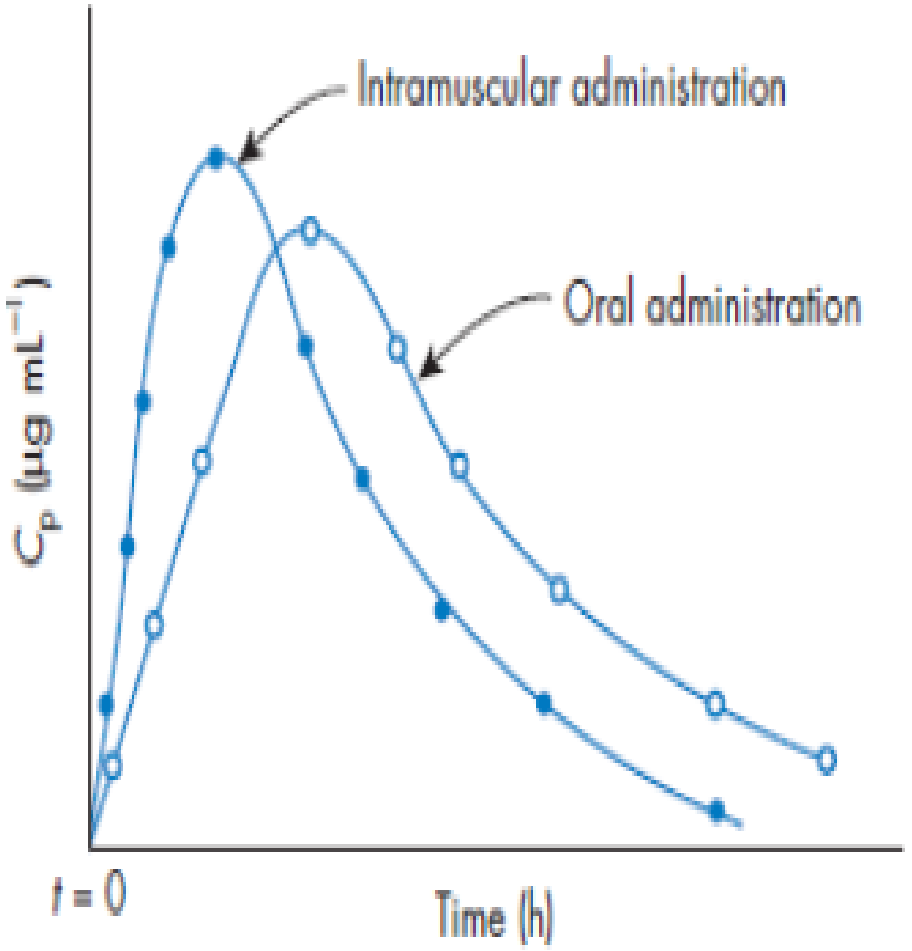
- After oral administration, absorbed drug travels through the portal circulation to the liver before reaching the systemic circulation.
- Drug metabolism in the intestinal wall or liver may reduce the amount of unchanged drug reaching the systemic circulation.

5. Formulation effects

- Excipients, coatings, particle size, and release characteristics can influence dissolution and absorption.

2- Relative Bioavailability

- **Relative bioavailability** compares the systemic availability of the same drug administered in two different formulations or under two different treatment conditions.
- Unlike absolute bioavailability, it does not require an intravenous reference.
- For example, a tablet may be compared with an oral solution, or a new formulation may be compared with an existing formulation.
- Relative bioavailability is useful during **formulation development** because it helps identify how formulation differences influence drug exposure



formula for Relative Bioavailability

- For two formulations, A and B:

$$F_{rel}(\%) = \frac{AUC_A \times D_B}{AUC_B \times D_A} \times 100$$

Where:

- F_{rel}: Relative bioavailability of formulation A compared with formulation B.
- AUC_A: AUC after administration of formulation A.
- AUC_B: AUC after administration of formulation B.
- D_A: Dose of formulation A.
- D_B: Dose of formulation B.

Formulation B is the reference for this calculation.

- If both formulations are administered at **the same dose**, the dose terms cancel.
- The equation simplifies to:

$$F_{rel}(\%) = \frac{AUC_A}{AUC_B} \times 100$$

Example

- A researcher compares a tablet with an oral solution containing the same drug.

Parameter	Tablet A	Solution B
Dose	200 mg	200 mg
AUC	90 mg·h/L	75 mg·h/L

$$F_{rel} = \frac{AUC_A}{AUC_B} \times 100$$

Calculate the relative bioavailability of the tablet compared with the solution.

$$F_{rel} = \frac{90}{75} \times 100$$

- The tablet produces **20% greater systemic exposure than the oral solution under the study conditions.**
- This finding does not automatically establish whether the formulations are bioequivalent.

$$F_{rel} = 120\%$$

Absolute versus Relative Bioavailability

Feature	Absolute bioavailability	Relative bioavailability
Purpose	Compares systemic availability with IV administration	Compares systemic availability between two formulations or conditions
Reference	Intravenous administration of the same drug	Another suitable formulation or treatment
Routes	Usually compares IV with a non-IV route	May compare products administered by the same route
Dose correction	Required when doses differ	Required when doses differ
Typical expression	Percentage of dose systemically available as unchanged drug	Percentage of exposure relative to the comparator
Can the result exceed 100%?	Not ordinarily, when correctly calculated under appropriate assumptions	Yes
Main applications	Estimating systemic availability and presystemic loss	Comparing formulations and assessing formulation-related changes

- **Absolute:** Compare with intravenous administration.
- **Relative:** Compare with another formulation or treatment.

Methods For Assessing Bioavailability

1.Pharmacokinetics methods:

a. Plasma level study

- Maximum plasma drug concentration (Cmax).
- Time to maximum plasma drug concentration (Tmax).
- Area under the plasma concentration–time curve (AUC).

b. Urinary excretion study

- Cumulative amount (Qu)
- Rate of renal excretion ($dQ\text{u}/dt$)
- Time for max. urinary excretion (t)

2. In Vivo Pharmacodynamics method

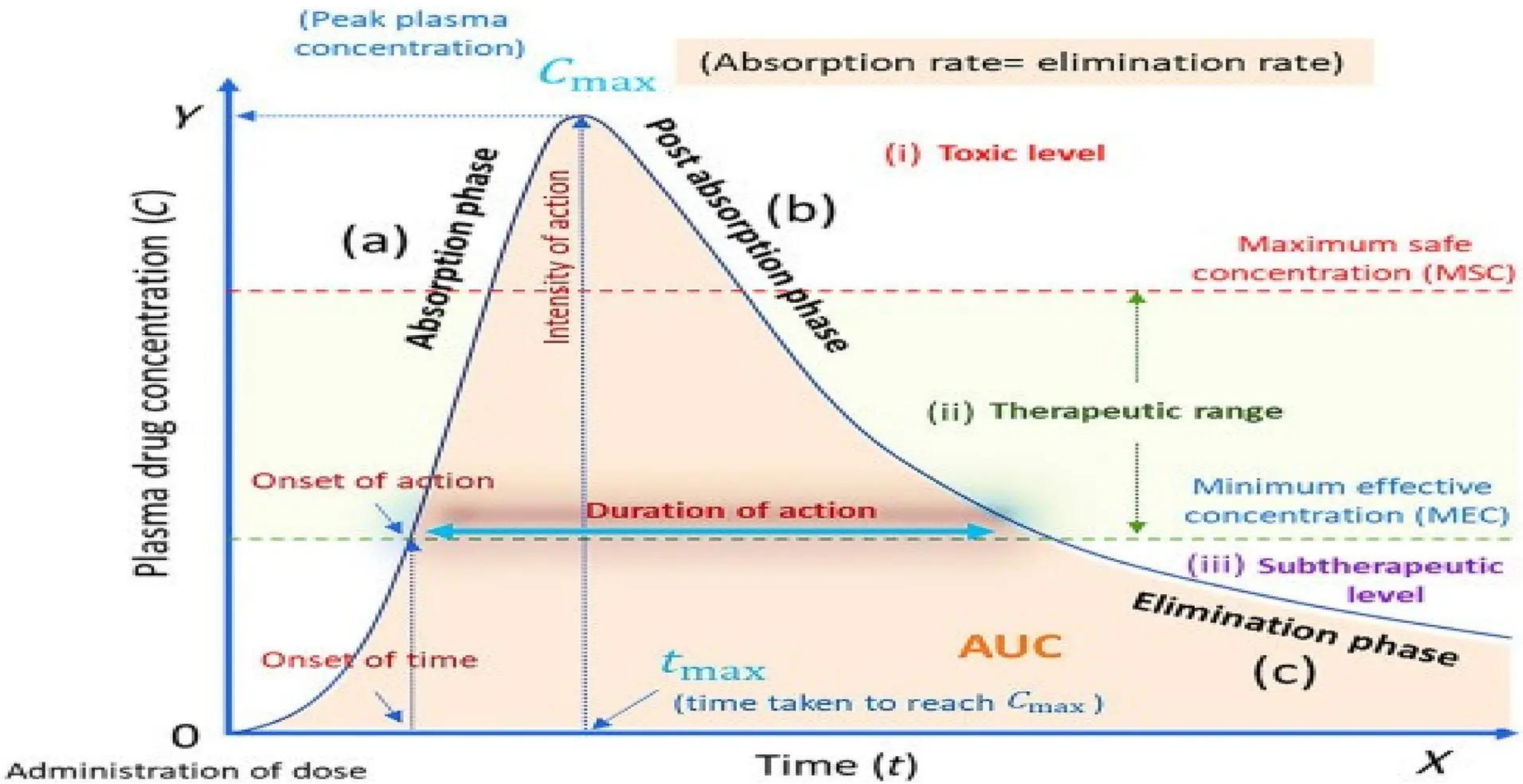
A. Acute pharmacological response (pupil diameter & ECG)

B. Therapeutic response (clinical response)

3. In-vitro Studies

- **Drug Dissolution**
  - Rapid rate of dissolution in vitro ⟹ Rapid rate of bioavailability in vivo

Plasma Drug Concentration–Time Curve



Comparison of C_{max}, T_{max}, and AUC

Parameter	Definition	Main information	Typical units
C_{max}	Maximum observed plasma concentration	Peak systemic exposure; often informative about absorption rate	mg/L, µg/mL, ng/mL
T_{max}	Time to maximum observed concentration	Approximate timing of peak exposure	Minutes or hours
AUC	Area under the plasma concentration–time curve	Extent of systemic exposure	Concentration × time

AUC.

- The ***area under the plasma level time curve*, AUC**, is a measurement of the ***extent*** of drug bioavailability .
- The AUC reflects the total amount of active drug that reaches the systemic circulation.
- The AUC is the area under the drug plasma level time curve from t = 0 to t =∞, and is equal to the amount of unchanged drug reaching the general circulation divided by the clearance.

Mathematical expression

- The total AUC from time zero to infinity is expressed as:

$$AUC_{0-\infty} = \int_0^{\infty} C_p(t)\, dt$$

- $C_p(t)$ is the plasma drug concentration at time t.
- t is time.

$$AUC = \frac{F \times D}{CL}$$

F = absolute bioavailability, expressed as a fraction.
D = administered dose.
CL = systemic clearance.

- For intravenous administration, F=1 , so:

$$AUC_{\mathrm{IV}} = \frac{D_{\mathrm{IV}}}{CL}$$

For oral administration:

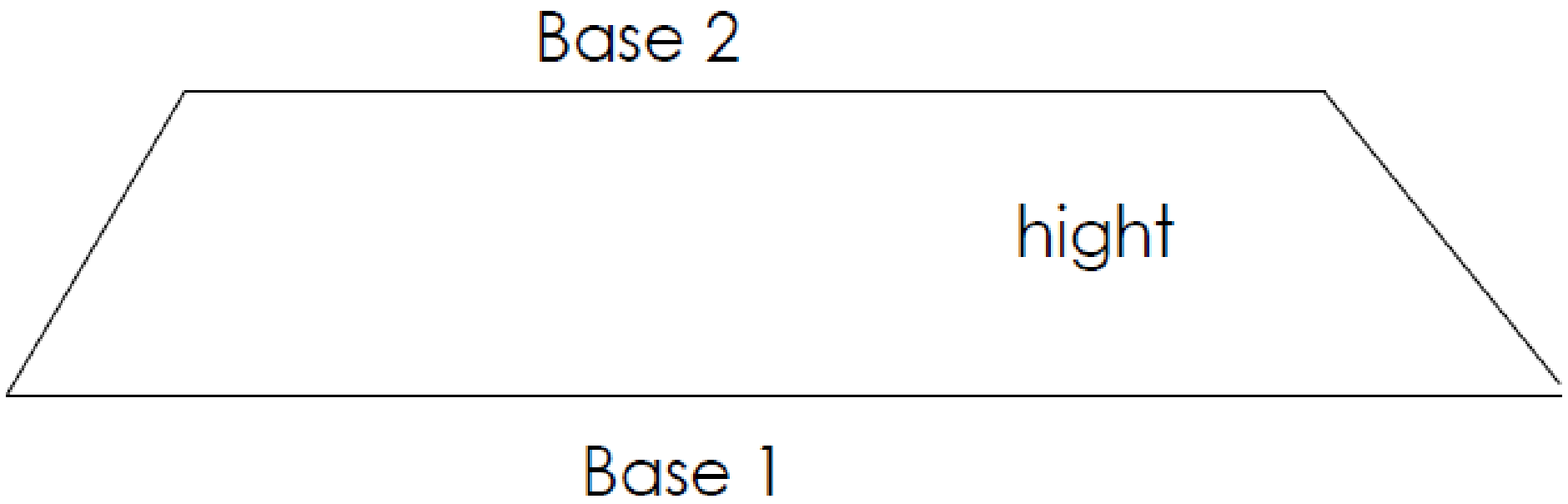
$$AUC_{\mathrm{oral}} = \frac{F \times D_{\mathrm{oral}}}{CL}$$

Methods for estimation of AUC for oral one compartment model (plasma)

Trapezoidal method

The area of a trapezoid = average height x base

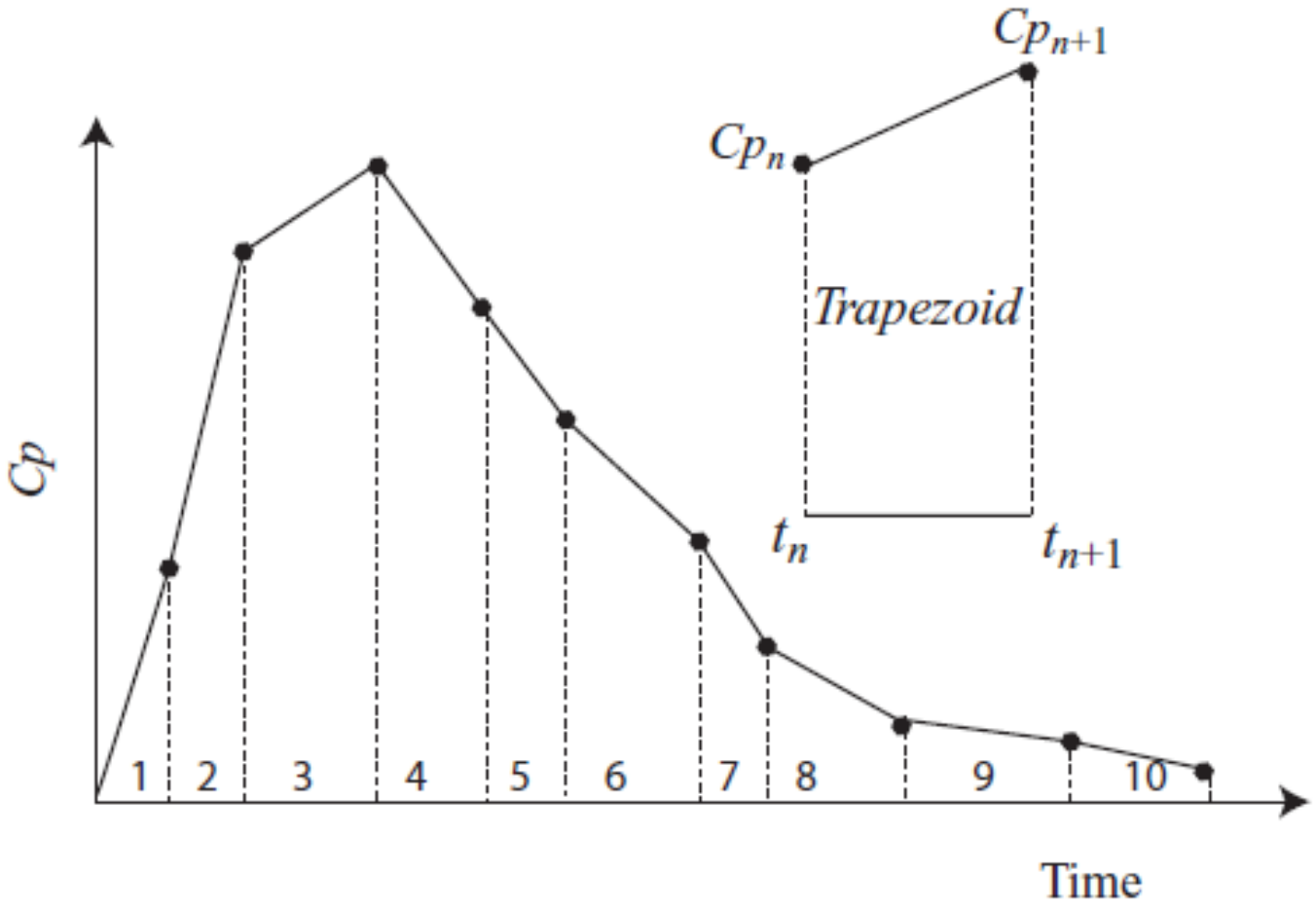
Area of trapezoid = $\frac{(base\ l + bas\ 2)}{2} . Hight$



Calculation of AUC by using the Trapezoidal Rule

The area of a trapezoid = average height x base

Area of trapezoid = $\frac{(Cp_2+Cp_1)}{2}.(t_2-t_1)$



$$AUC_x = \frac{Cp_n + Cp_{n+1}}{2} * (t_{n+1} - t_n)$$

$$AUC\ Cp_{last \to \infty} = \frac{Cp_{last}}{K}$$

- *After oral administration the concentration of the drug at zero time is zero thus simply the* ***first area is =*** $\frac{(Cp_2+0)}{2}.(t_2-0)$
- 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

Units of AUC

- **Con. * time**

example : Mg. hr / L

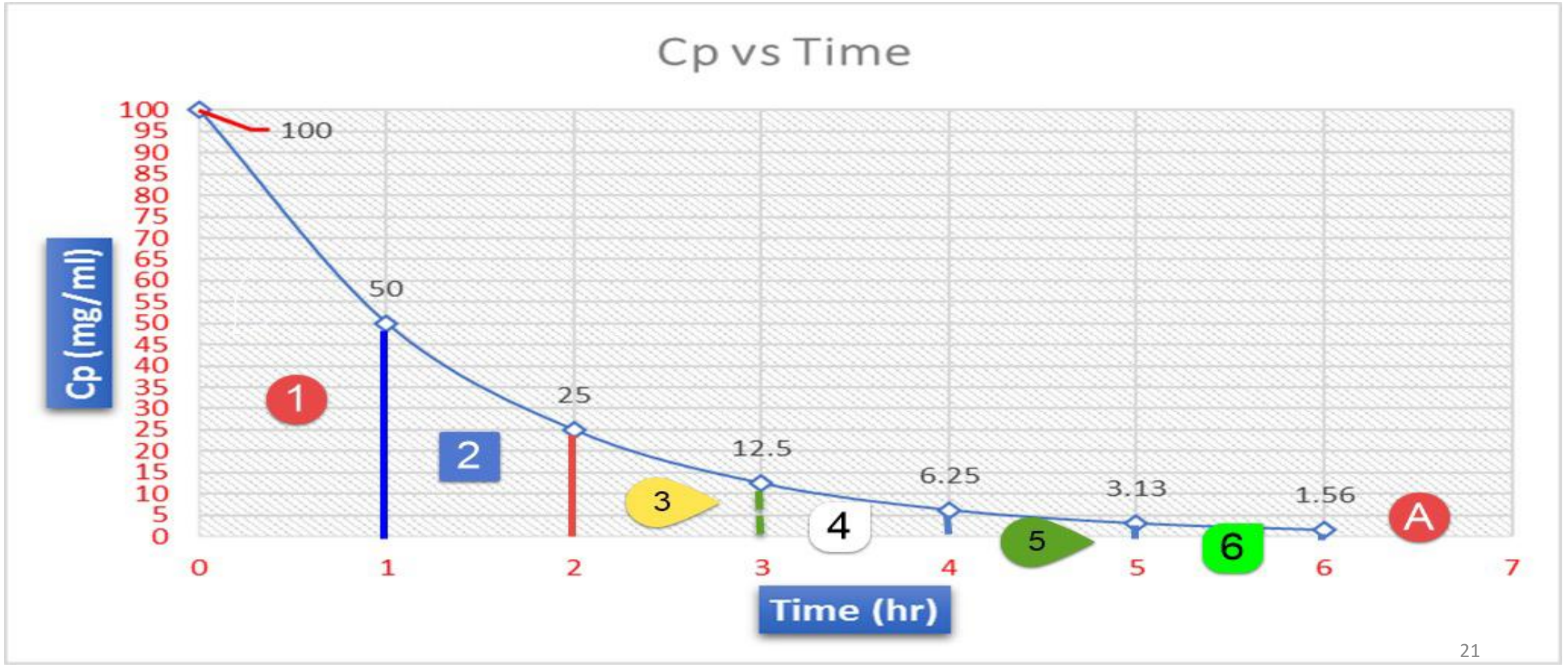
***Example**: Calculation of AUC Using the Trapezoidal Rule for the following data:*

Time (hr))	0	1	2	3	4	5	6
C_t (mg/L)	100	50	25	12.5	6.25	3.13	1.56

Solution: Step 1

1. Plot the curve and

2. Determine segment



Step 2:

1. Calculate each segment and

2. Collect AUC from zero to Cp_{last}

$$AUC = \frac{Cp_n + Cp_{n+1}}{2} * (t_{n+1} - t_n)$$

- $AUC_1 = \frac{100+50}{2} \times (1 - 0)$
- $= \frac{150 \frac{mg}{L}}{2} \times 1\ hr$
- $AUC_1 = 75\ mg.hr/L$

No. AUC	Ct (mg/L)	Area (mg.hr/L)
1	50	75
2	25	37.5
3	12.5	18.75
4	6.25	9.375
5	3.13	4.688
6	1.56	2.344
$\sum AUC_{0 \rightarrow last}$		**147.657**

Step 3: Calculate AUC from Cp_{last} to infinity by two stages

1. Determine the K

$$\text{Log C}_0 - \log C_t = \frac{\text{Kt}}{2{\cdot}3}$$

$$\text{Log } 3.13 - \log 1.56 = \frac{\text{K6}}{2{\cdot}3}$$ **K=** 0.115

2. Determine AUC_{last}

AUC_{last} = 1.56/0.115=13.5 $mg.$ hr / L

$$[AUC]_0^{\infty} = \sum [AUC]_{t_{n+1}}^{t_n} + \frac{Cp_{last}}{K}$$

AUC = 147.657 + 13.5= 161.1 $mg.$ hr / L

Bioequivalence Studies in New Drug Development

- During new drug development, the formulation used in **clinical trials** may differ from the final marketed product. Different dosage forms, such as capsules and tablets, may produce different drug absorption profiles.

Purpose:

- To demonstrate that the commercial formulation performs comparably to the formulation used in clinical studies.

Example:

- If a drug is initially tested as a capsule but marketed as a tablet, comparative studies may be required to establish comparable drug exposure.

Bioequivalence Studies in Generic Drug Development

- Generic drugs contain the same active ingredient as their reference products and must meet applicable regulatory requirements for pharmaceutical quality and equivalence.

Example:

- Two tablets containing 250 mg of the same drug may not have the same absorption profile. Bioequivalence studies compare drug exposure from the generic (**test product**) with that from the reference product.
- The same active ingredient and dose alone do not establish bioequivalence.

Bioequivalence Studies After Product Approval

- Changes in formulation, raw material suppliers, manufacturing processes, equipment, production sites, or production scale may affect drug dissolution, stability, and absorption.
- To determine whether a product maintains acceptable performance after manufacturing or formulation changes.

Possible assessments:

- Comparative dissolution studies, bioequivalence studies, or other appropriate evaluations, depending on the change and applicable regulatory guidance.

Example:

- Changing a tablet's granulation process may alter its porosity and dissolution rate, potentially affecting drug absorption.

FDA uses the following terms to define the type or level of equivalency between drug products:

- **Pharmaceutical equivalents** are drug products that **contain identical amounts of the identical active ingredient**, that is, the **same salt** or ester of the **same therapeutic moiety**, in **identical dosage forms** but **not necessarily containing the same inactive ingredients**.
- **Pharmaceutical alternatives** are **drug products** that contain the **identical therapeutic moiety** or its precursor but **not necessarily in the same amount or dosage form** or as **the same salt or ester.**
  - **(e.g., tetracycline hydrochloride, 250 mg capsules vs. tetracycline phosphate complex, 250 mg capsules; quinidine sulfate, 200 mg tablets vs. quinidine sulfate, 200 mg capsules)**
- **Bioequivalent drug products are pharmaceutical equivalents or pharmaceutical alternatives** whose **rate and extent of absorption are similar**.
- **Therapeutic equivalents:** used to indicate pharmaceutical equivalents that provide **the same therapeutic effect** when administered to **the same individuals in the same dosage regimens.**

- **The most common experimental plan to compare the bioavailability of two drug products: is a simple crossover design study.**
  - **12 to 24** individuals carefully matched subjects (usually healthy men aged 18 to 40 years and having similar height and weight) are administered **both products** under fasting conditions.
  - each test subject is randomly assigned one of the two products for the **first phase** of the study.
  - Once the first assigned product is administered, **samples of blood or plasma are drawn** from the subjects at predetermined times and analyzed for the active drug moiety and its metabolites as a function of time.
  - The same procedure is then repeated (crossover) with the **second product** after an appropriate interval, that is, a washout period to ensure that there is no residual drug from the first administered product that would artificially inflate the test results of the second product.
  - Afterward, the patient population data are tabulated and the parameters used to assess and compare bioavailability; that is, C_{max}, T_{max}, and AUC are analyzed with statistical procedures.
  - The value of the crossover experiment is that each individual serves as his own control by taking each of the products. Thus, inherent differences between individuals are minimized.

- According to the FDA: *generic drug is considered* ***bioequivalent if the rate and extent of absorption do not show a significant difference from that of the standard drug when administered at the same molar dose of the therapeutic ingredient under the same experimental conditions***.
- To gain FDA **approval** **a generic drug product** must have these characteristics:
    1. **The same active ingredients** as the standard drug.
    2. **Identical strength**, **dosage form**, and **route of administration**
    3. The **same indications** and **precautions** for use.
- The sampling time for blood and/or urine is usually at least three times the half-life of the active drug ingredient or therapeutic moiety, its metabolite(s)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