Bioavailability and Bioequivalence

Session Objectives

- @ the end of this session you will be able to:
  - Define terms related with therapeutic and pharmaceutical substitution.
  - Describe and compute relative and absolute bioavailabilities
  - Identify methods for the assessment of bioavailability

Introduction

- **A multisource drug product** is a drug product that contains the same active drug substance in the same dosage form and is marketed by more than one pharmaceutical manufacturer.

- **Single-source drug products** are drug products for which the patent has not yet expired or has certain exclusivities so that only one manufacturer can make it.

  - Brand-name (innovator) drug products.

Definitions

- **Bioavailability:** is the rate and extent to which the active ingredient is absorbed from a drug product and becomes available at the site of action.

- **Bioequivalent drug products:** pharmaceutical equivalent or pharmaceutical alternative products that display **comparable bioavailability** when studied under similar experimental conditions.

- **Brand name**: The trade name of the drug, is privately owned by the manufacturer or distributor and is used to distinguish the specific drug product from competitor's products (eg, **Tylenol**, McNeil Laboratories).

- **Chemical name**: The name used by organic chemists to indicate the chemical structure of the drug (eg, **N-acetyl-*p*-aminophenol**).

- **Generic name**: The established, nonproprietary, or common name of the active drug in a drug product (eg,acetaminophen).

- **Equivalence:** Relationship in terms of BA, therapeutic response, or a set of established standards of one drug product to another.

- **Generic substitution:** The process of dispensing a different brand or an unbranded drug product in place of the prescribed drug product.
- The substituted drug product contains the same active ingredient or therapeutic moiety as the same salt or ester in the same dosage form but is made by a **different manufacturer**.
  - E.g., a prescription for **Motrin**® brand of ibuprofen might be dispensed by the pharmacist as **Advil**® brand or as a non branded generic **ibuprofen**

- **Pharmaceutical alternatives**: Drug products that contain the same therapeutic moiety but as different salts, esters, or complexes.
  - E.g., **tetracycline phosphate** or **tetracycline HCl** equivalent to 250 mg tetracycline base are considered pharmaceutical alternatives.

- Different **dosage forms** and **strengths** within a product line by a **single manufacturer** are pharmaceutical alternatives.
  - E.g., an **extended-release dosage form** and a standard **immediate-release dosage form** of the same active ingredient.
  - The FDA currently considers a **tablet** and **capsule** containing the same active ingredient in the same dosage strength as pharmaceutical alternatives.

- **Pharmaceutical equivalents:** Drug products in identical dosage forms that contain the same:
  - Active ingredient(s)
  - Salt or ester
  - Dosage form
  - Route of administration
  - Strength
- But they may differ in:
  - Characteristics such as shape,, release mechanisms, packaging
  - Excipients (including colors, flavors, preservatives)
  - Expiration time
  - Labeling (to some extent)

- **Pharmaceutical substitution:** The process of dispensing a **pharmaceutical alternative** for the prescribed drug product.

  - Ampicillin suspension → ampicillin capsules

  - Tetracycline hydrochloride → tetracycline phosphate

    - Requires the physician's approval.

- **Therapeutic alternatives:** Drug products containing **different active ingredients** that are indicated for the same therapeutic or clinical objectives.

- Active ingredients in therapeutic alternatives are from the **same pharmacologic class** and are expected to have the same therapeutic effect when administered to patients for such condition of use.
  - Ibuprofen → aspirin;
  - Cimetidine → ranitidine.

- **Therapeutic equivalents:** Drug products are considered to be therapeutic equivalents only if they are the **same clinical effect and safety profile**.

✍**Therapeutic substitution:** The process of dispensing a **therapeutic alternative** in place of the prescribed drug product.

- Amoxicillin → ampicillin
- Ibuprofen → aspirin

Relative and Absolute Availability

- **Relative Availability**

Relative (apparent) availability is the availability of the drug from a drug product as compared to a recognized standard.

The relative availability of two drug products given at the same dosage level and by the same route of administration can be obtained using the following equation:

$$\text{Relative availability} = \frac{[\text{AUC}]\text{A}}{[\text{AUC}]\text{B}}$$

Where drug product B is the recognized reference standard.

- When different doses are administered, a correction for the size of the dose is made, as in the following equation:

$$\text{Relative availability} = \frac{[\text{AUC}]\text{A}/\text{dose A}}{[\text{AUC}]\text{B}/\text{dose B}}$$

- **Urinary drug excretion data** may also be used to measure relative availability, as long as the total amount of intact drug excreted in the urine is collected.

$$\text{Relative availability} = \frac{[Du]^{\infty}A}{[Du]^{\infty}B}$$

Where $[D_u]^{\infty}$ is the total amount of drug excreted in the urine

- **Absolute Availability**
  - The absolute availability of drug is the systemic availability of a drug after extravascular administration (eg, oral, rectal, transdermal, subcutaneous) compared to **IV dosing**.

  - Absolute availability after oral drug administration using plasma data can be determined as follows

$$\text{Absolute availability} = F = \frac{[AUC]PO/\text{dose PO}}{[AUC]IV/\text{dose IV}}$$

- Absolute availability using urinary drug excretion data can be determined by the following:

$$\text{Absolute availability} = \frac{[Du]_{\infty}\,PO/\text{dose PO}}{[Du]_{\infty}\,IV/\text{dose PO}}$$

Example:

- The bioavailability of a new investigational drug was studied in 12 volunteers. Each volunteer received either a single oral tablet containing 200 mg of the drug, 5 mL of a pure aqueous solution containing 200 mg of the drug, or a single IV bolus injection containing 50 mg of the drug. Plasma samples were obtained periodically up to 48 hours after the dose and assayed for drug concentration. The average AUC values (0–48 hours) are given in the table below.

Drug Product	**Dose (mg)**	**AUC (mg hr/mL)**	Standard Deviation
Oral tablet	200	89.5	19.7
Oral solution	200	86.1	18.1
IV bolus injection	50	37.8	5.7

From these data, calculate

1. The **relative bioavailability** of the drug from the oral solution compared to the tablet and
2. The **absolute bioavailability** of the drug from the tablet.

- **Relative availability** = [AUC]A/[AUC]B

  = 86.1/89.5

  = 0.962

  = 96.2%

- **Absolute availability**

  $= \left([AUC]_{Tab}/Dose_{Tab}\right)/\left([AUC]IV/Dose_{IV}\right)$

  = (89.5/200)/(37/ 50)

  = 0.4475/0.756

  = 0.592

  = 59.2%

- Because *F*, the fraction of dose absorbed from the tablet, is less than 1, the drug is not completely absorbed systemically, as a result of either poor absorption or metabolism by first-pass effect.

- The relative bioavailability of the drug from the tablet is approximately 100% when compared to the oral solution.

- It is possible for the relative bioavailability to be greater than 100%.

	Plasma Concentration (mg/ml)			
Time after Dose (hr)	**IV** Sol (2 mg/kg)	Oral **Solution** (10 mg/kg)	Oral **Tablet** (10 mg/kg)	Oral **Capsule** (10 mg/kg)
0.5	5.94	23.4	13.2	18.7
1.0	5.30	26.6	18.0	21.3
1.5	4.72	25.2	19.0	20.1
2.0	4.21	22.8	18.3	18.2
3.0	3.34	18.2	15.4	14.6
4.0	2.66	14.5	12.5	11.6
6.0	1.68	9.14	7.92	7.31
8.0	1.06	5.77	5.00	4.61
10.0	0.67	3.64	3.16	2.91
12.0	0.42	2.30	1.99	1.83
AUC	29.0	145.0	116.0	116.0

a) Which of the three oral drug products would be preferred as a reference standard for the determination of relative bioavailability? Why?

b) From which oral drug product is the drug absorbed more rapidly?

c) What is the absolute bioavailability of the drug from the oral solution?

d) What is the relative bioavailability of the drug from the oral tablet compared to the reference standard?

Objectives of Bioavailability studies

- BA studies are important in the:-
  - Primary stages of development of a suitable DF for a new drug entity
  - Determination of influence of excipients, patient related factors and possible interaction with other drugs on the efficiency of absorption
  - Development of new formulations of the existing drugs
  - Control of quality of a drug product during the early stages of marketing

    →Determine the influence of processing factors, storage and stability on drug absorption

Methods of Assessing Bioavailability

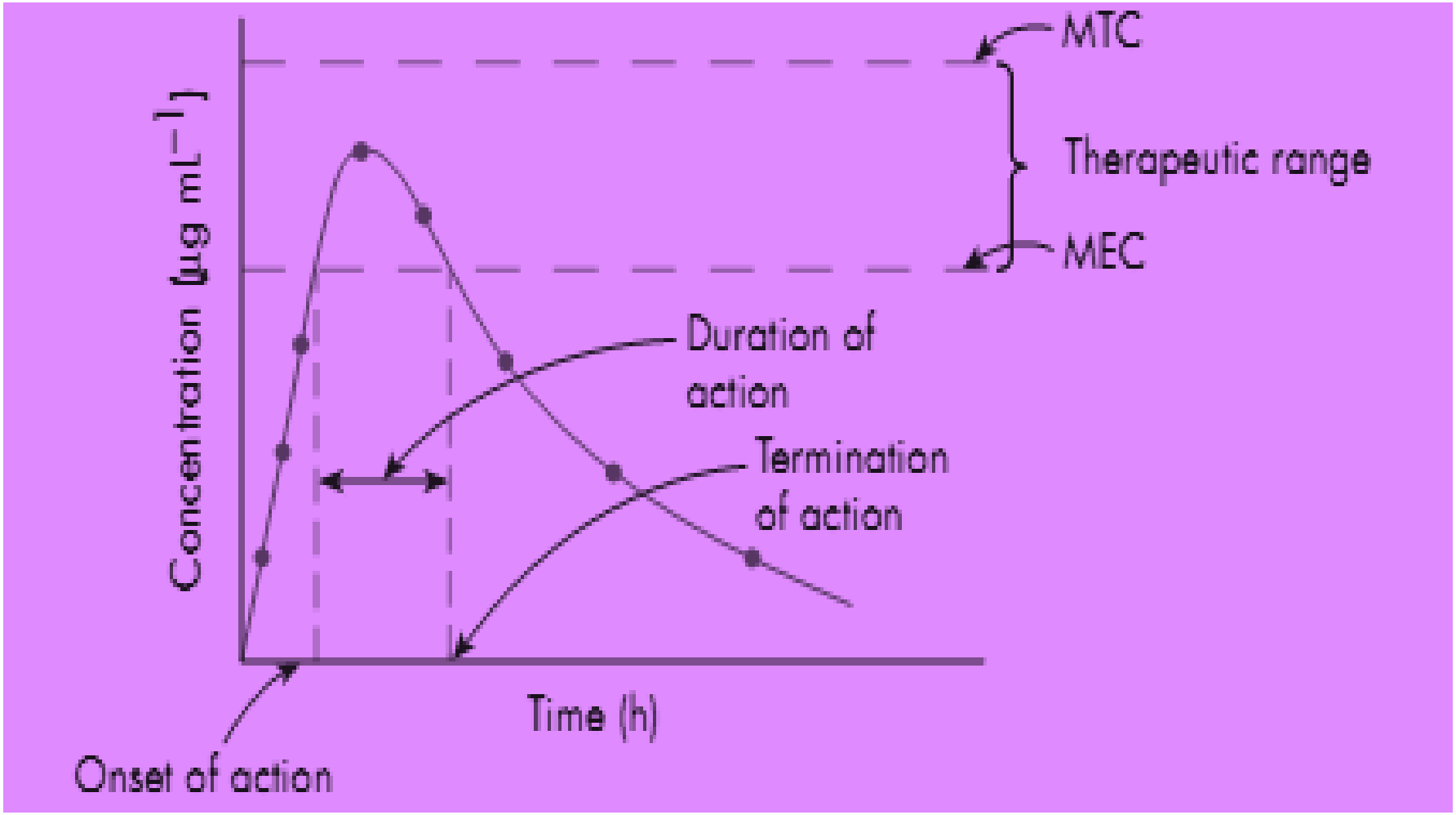
- Different methods are used to assess drug bioavailability

- ***Plasma drug concentration data***
  - Time for peak plasma concentration (tmax)
  - Peak plasma drug concentration (Cmax)
  - Area under plasma drug concentration–time curve (AUC)

- **Urinary drug excretion data**
  - Cumulative amount of drug excreted in urine(Du_∞)
  - Rate of drug excretion in urine (dDu/dt)
  - Time for maximum urinary excretion (t_∞)

Plasma concentration-time curves

- When a single dose of a drug is administered orally to a patient, serial blood samples are withdrawn and the plasma assayed for drug concentration at specific periods of time after administration, a **plasma concentration-time curve can be constructed.**


MTC
Therapeutic range
MEC
Concentration (μg mL⁻¹)
Duration of action
Termination of action
Time (h)
Onset of action

- **Absorption Phase**

- At zero time → the concentration of drug in the plasma will be zero

- As the tablet passes into the stomach and/or intestine it disintegrates, the drug dissolves and absorption occurs.

- Initially the concentration of drug in the plasma rises, as the **rate of absorption exceeds the rate at which the drug is being removed by distribution and elimination**

- **Peak Concentration**

  - This represents the highest conc. of the drug achieved in the plasma.

  - It is reached when **the rate of appearance of drug in the plasma is equal to its rate of removal by distribution and elimination.**

- **Elimination phase:**

  - Eventually drug absorption ceases when the bioavailable dose has been absorbed, and the concentration of drug in the plasma is now controlled only by its rate of elimination by metabolism and/or excretion.

- **Minimum effective (or therapeutic) plasma concentration:** The concentration of drug in the plasma below which no therapeutic effects of the drug occur

- **Maximum safe concentration**: The concentration of drug in the plasma above which side-effects or toxic effects occur

- **Therapeutic range or window:** A range of plasma drug concentrations in which the desired response is obtained yet toxic effects are avoided

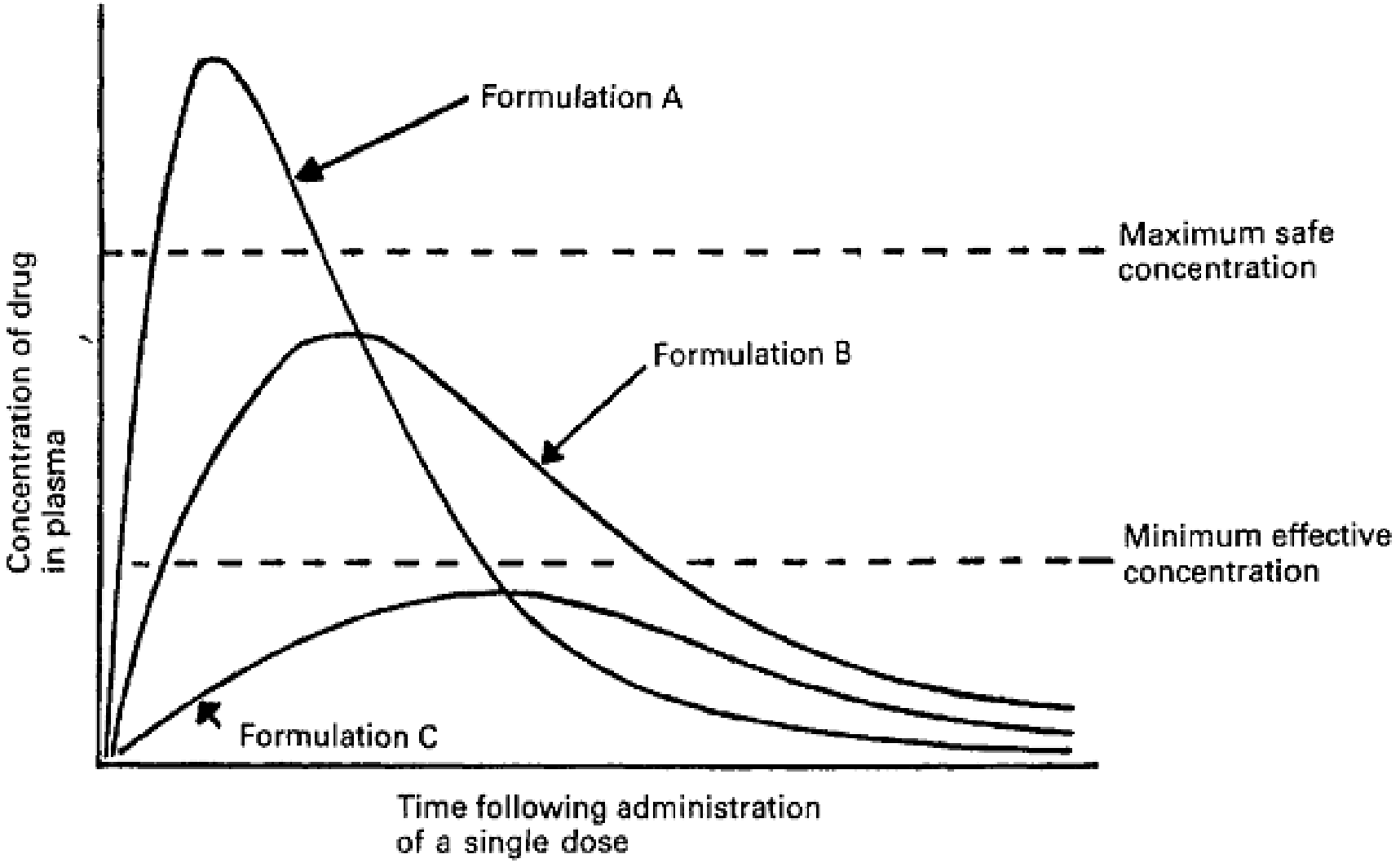
- **Onset:** The time required to achieve the minimum effective plasma concentration following administration of the dosage form.

- **Duration**: is the period during which the concentration of drug in the plasma exceeds the minimum effective plasma concentration.

- **Time of peak concentration:** This is the period of time required to achieve the peak plasma concentration of drug after the administration of a single dose.

The Use of Plasma Concentration-Time Curves in Bioavailability Studies

- Let us see the administration of single equal doses of three different formulations, **A**, **B** and **C**, of the same drug to the same healthy individual by the same route of administration on three separate occasions can be considered


Formulation A
Maximum safe concentration
Formulation B
Minimum effective concentration
Formulation C
Concentration of drug in plasma
Time following administration of a single dose

- The differences between the three curves are attributed solely to differences in the **rate and/or extent of absorption** of the drug from each formulation.

  ⇗ The **AUCs** for formulation A and B are similar

  ➲ The drug is absorbed to a similar extent from these two formulations.

- Formulation A shows a **fast onset** of therapeutic action, but as its peak plasma concentration exceeds the maximum safe concentration →**toxic side-effects**.

- Formulation B, which gives a slower rate of absorption than A, shows a slower therapeutic onset than A, but its peak plasma concentration lies within the therapeutic range

- Formulation C gives a much smaller area under the plasma concentration-time curve, indicating that a lower proportion of the dose has been absorbed.

↳Results in the peak plasma concentration not reaching the minimum effective concentration

➲Does not produce a therapeutic effect and consequently is clinically ineffective as a single dose.

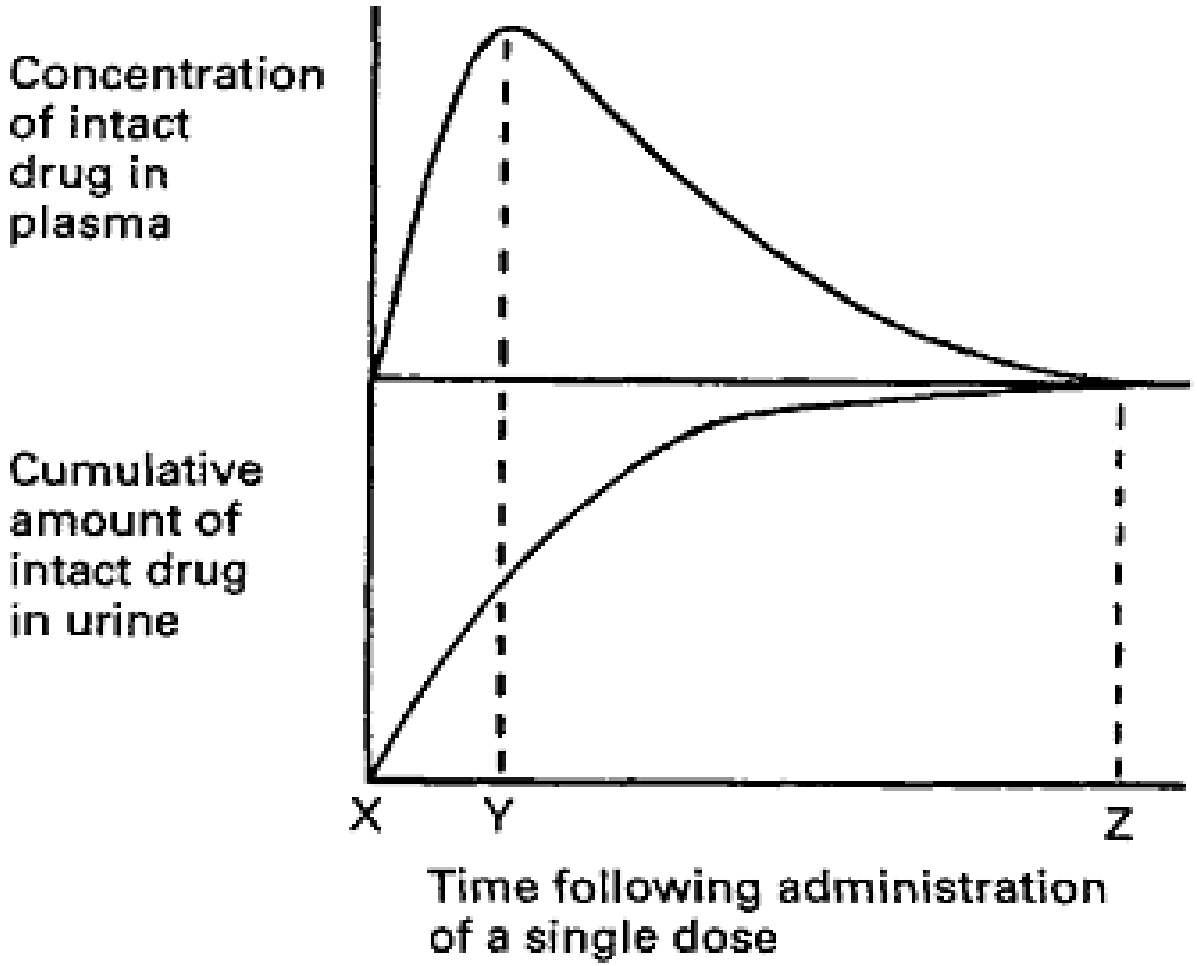
Cumulative Urinary Drug Excretion Curves

- Measurements involving metabolite levels in the urine are only valid when the drug in question is not subject to metabolism prior to reaching the systemic circulation.

- The assessment of BA by urinary excretion is based on the assumption that the appearance of the drug and/or its metabolites in the urine is a function of the rate and extent of absorption.

- The important parameters in urinary excretion studies are **the cumulative amount of intact drug** and/or metabolites excreted, and the **rate** at which this excretion takes place.

- A cumulative urinary excretion curve is obtained by collecting urine samples (resulting from total emptying of the bladder) at known intervals after a single dose of the drug has been administered.


Concentration of intact drug in plasma
Cumulative amount of intact drug in urine
X
Y
Z
Time following administration of a single dose

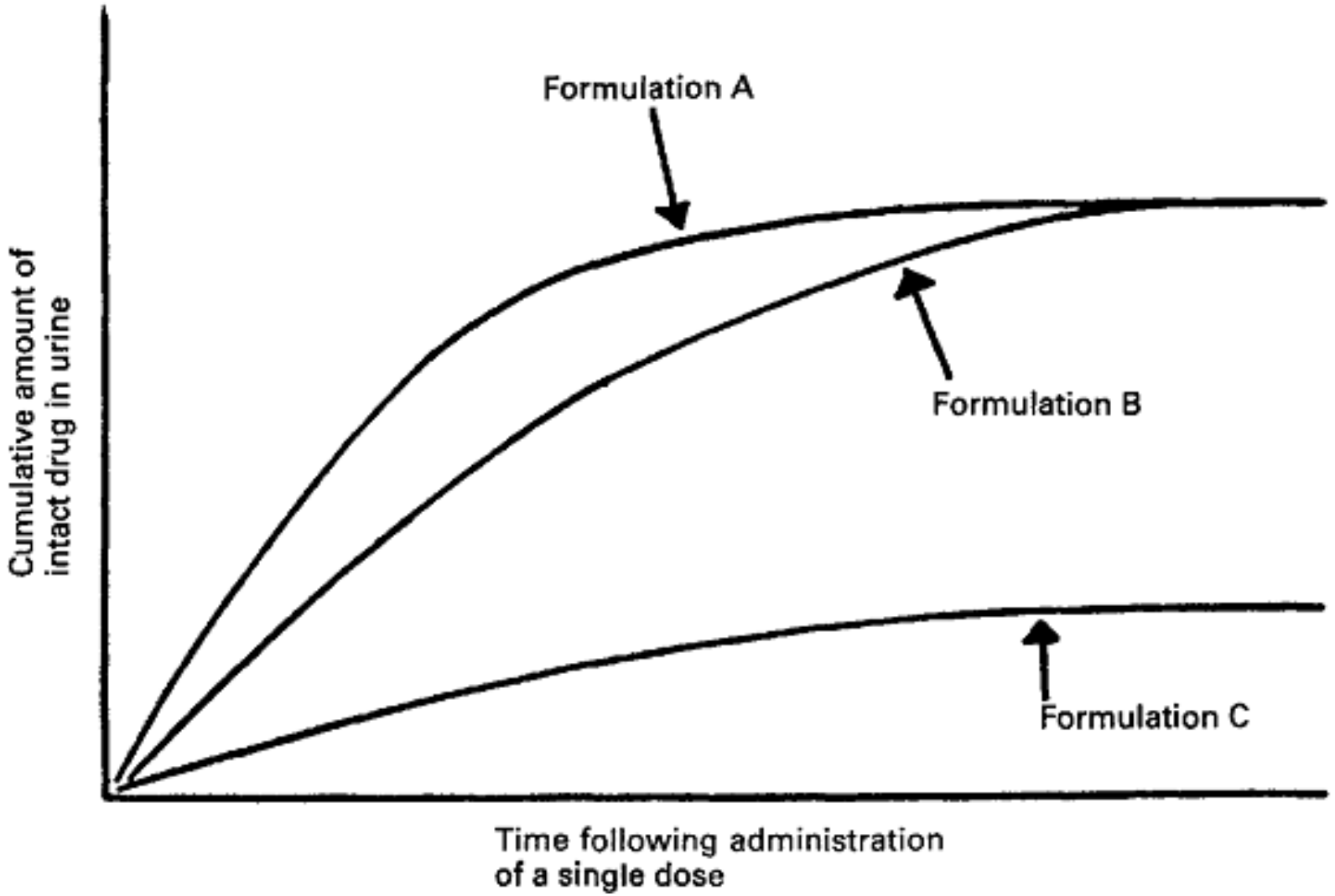
- The initial segments **(X-Y)** of the curves reflect the 'absorption phase' (i.e. where absorption is the dominant process)

- The total amount of intact drug (and/or its metabolite) excreted in the urine at point Z corresponds to the time at which the plasma concentration of intact drug is zero and essentially all the drug has been eliminated from the body.

- The total amount of drug excreted at **point Z** may be quite different from the total amount of drug administered (i.e. the dose), either because of:
  - Incomplete absorption or
  - The drug being eliminated by processes other than urinary excretion.

The Use of Urinary Drug Excretion Curves in Bioavailability Studies

- Following the administration of single equal doses of three different formulations, A, B and C, of the same drug to the same healthy individual by the same extravascular route on three different occasions


Formulation A
Formulation B
Formulation C
Cumulative amount of intact drug in urine
Time following administration of a single dose

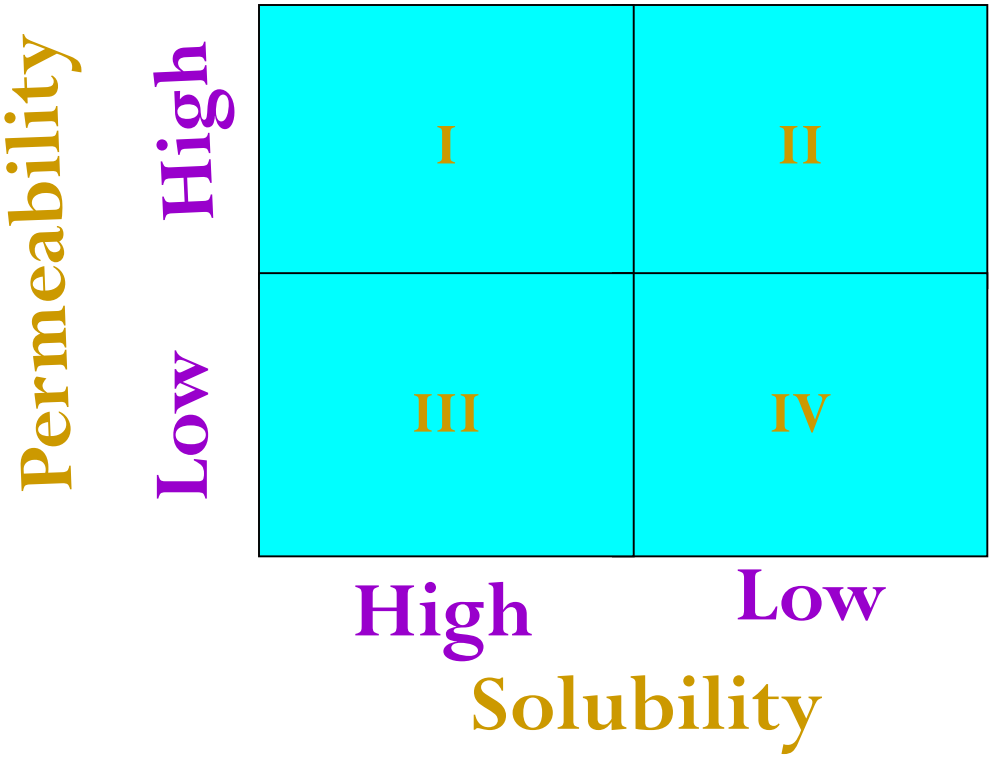
- **The rate of appearance** of drug in the urine from formulation A is faster than from B, the total amount of drug eventually excreted from these two formulations is the same.
  - The cumulative urinary excretion curves for formulations A and B eventually meet and merge

- The cumulative urinary excretion curve suggests that both the rate and extent of drug absorption are reduced in the case of formulation C

THE BIOPHARMACEUTICAL CLASSIFICATION SCHEME

- A biopharmaceutical classification scheme classifies drugs into four classes according to:
  - **Solubility** across the GI pH range and
  - **Permeability** across the GI mucosa

- According to the BCS, drug substances are classified into
  - **Class I** – High Permeability, High Solubility
  - **Class II** - High Permeability, Low Solubility
  - **Class III** – Low Permeability, High Solubility
  - **Class IV** – Low Permeability, Low Solubility



- A drug is considered to be highly soluble where the highest dose strength is soluble in 250 mL or less of aqueous media over the pH range 1-8.

- The volume is derived from the minimum volume anticipated in the stomach when a dosage form is taken in the fasted state with a glass of water.

- If the volume of aqueous media taken to dissolve the drug in pH conditions ranging from 1 to 8 is greater than 250 mL then the drug is considered to have low solubility.

- A drug is considered to be highly permeable when the extent of absorption in humans is expected to be greater than 90% of the administered dose.

Class I drugs

- These drugs will **dissolve rapidly** when presented in immediate-release dosage forms, and are also **rapidly transported** across the gut wall.

- unless they form insoluble complexes, are unstable in gastric fluids or undergo presystemic clearance

- Examples: the **b**-blockers propranolol and metoprolol.

Class II drugs

- For drugs in class II the **dissolution rate** is liable to be the rate-limiting step in oral absorption.
- This class of drug should be amenable to formulation approaches to improve the dissolution rate and hence oral bioavailability.
- Examples: ketoprofen and carbamazepine.

Class III drugs

- These drugs are those that **dissolve rapidly** but which are poorly permeable;
- Examples: ranitidine and atenolol.

Class IV drugs

- Are poorly soluble and poorly permeable.
- These drugs are liable to have poor oral bioavailability, or the oral absorption may be so low that they cannot be given by the oral route.
- Examples: **hydrochlorothiazide** and **frusemide**
- To improve systemic absorption: Forming prodrugs finding an alternative route of delivery

Summary???