تفريغ بيوفارما

اسم الموضوع: Bioavailability

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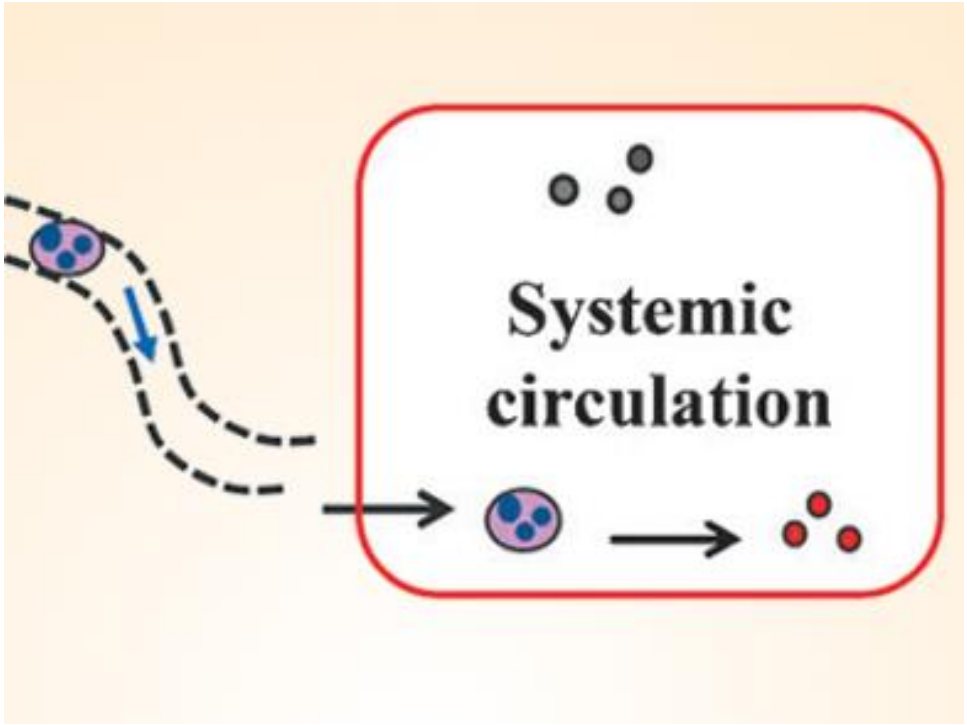
لجان الدُّفعات

Bioavailability



Introduction

- The most important property of any non-intravenous dosage form, intended to treat a systemic condition, is the ability to deliver the active ingredient to the bloodstream in an amount sufficient to cause the desired response
- This property of a dosage form has historically been identified as physiologic availability, biologic availability or bioavailability
- Bioavailability captures two essential features, namely how fast the drug enters the systemic circulation (**rate of absorption**) and how much of the nominal strength enters the body (**extent of absorption**)

Introduction

- Given that the therapeutic effect is a function of the drug concentration in a patient's blood, these two properties of non-intravenous dosage forms are, in principle, important in identifying the response to a drug dose:

1. Onset of response is linked to the rate of drug absorption whereas the time-dependent
2. Extent of response is linked to the extent of drug absorption.

Introduction

- Bioavailability following oral doses may vary because of either patient-related or dosage-form-related factors
- Patient factors can include the nature and timing of meals, age, disease, genetic traits and gastrointestinal physiology
- The dosage form factors include:

1) the chemical form of the drug (e.g. salt vs. acid),

2) its physical properties (e.g. crystal structure, particle size),

3) an array of formulation (e.g. non-active ingredients) and manufacturing (e.g. tablet hardness) variables.

The Importance of Bioavailability Studies

- In the strict sense, bioavailability studies provide an **estimate of the fraction of the orally administered dose** that is absorbed into the systemic circulation when compared to the bioavailability for a solution, suspension, or intravenous dosage form that is completely available
- Bioavailability studies provide other useful information that is important to **establish dosage regimens** and to support drug labeling, such as distribution and elimination characteristics of the drug
- Bioavailability studies provide indirect information regarding the **presystemic and systemic metabolism** of the drug and the role of transporters such as p-glycoproteins

The Importance of Bioavailability Studies

- Bioavailability studies designed to study the food effect provide information on **the effect of food** and other nutrients on the absorption of the drug substance

- Such studies when designed appropriately provide information on the **linearity or nonlinearity in the pharmacokinetics** of the drug and the dose proportionality

- Bioavailability studies provide information regarding the **performance of the formulation** and subsequently are a means to document product quality

Bioavailability Assessment Methods

1. Direct measure of bioavailability: → تدخل دورة الدموية Systemic Circulation plasma

- ***Based on Plasma Drug Concentrations:*** Drug concentrations in the blood and plasma are the most direct methods of determining the systemic availability of a drug

2. Indirect measure of bioavailability

- ***Based on Urinary Excretion Data:*** This method can be used only if urinary excretion of unchanged drug is the main mechanism of elimination of the drug and urine samples have been collected in intervals as short as possible to measure the rate and amount of excretion as accurately as possible
- ***Based on Acute Pharmacodynamics Effect:*** This approach may be applicable when the drug is not intended to be delivered into the bloodstream for systemic availability. It is an indirect measure of bioavailability in cases where the analytical method for assessing drug concentrations in the plasma or other biological fluids cannot be developed.

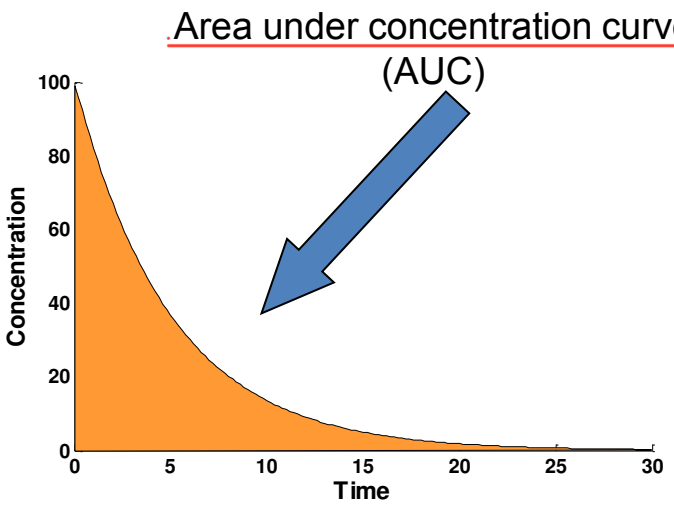
Absolute Bioavailability

- **Absolute bioavailability** of a drug is the systemic availability of the drug after extravascular administration of the drug and is measured by comparing the area under the drug concentration–time curve after extravascular administration to that after IV administration

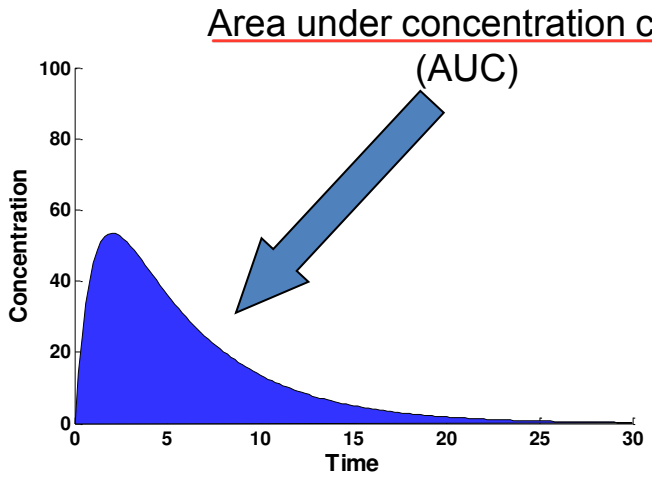
Bioavailability 100%

- Extravascular administration of the drug comprises routes such as oral, rectal, subcutaneous, transdermal, nasal, etc.

IV bolus



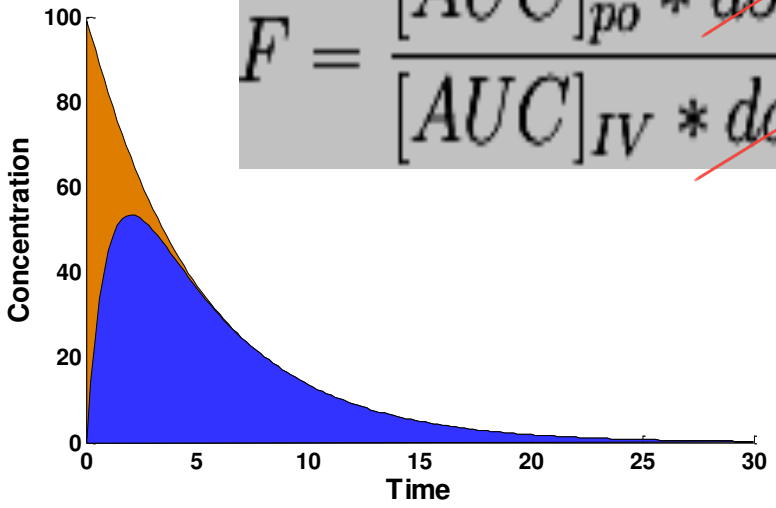
Oral dosage form (product A)



Absolute bioavailability

For the different doses (IV vs. Oral), the bioavailability is given by:

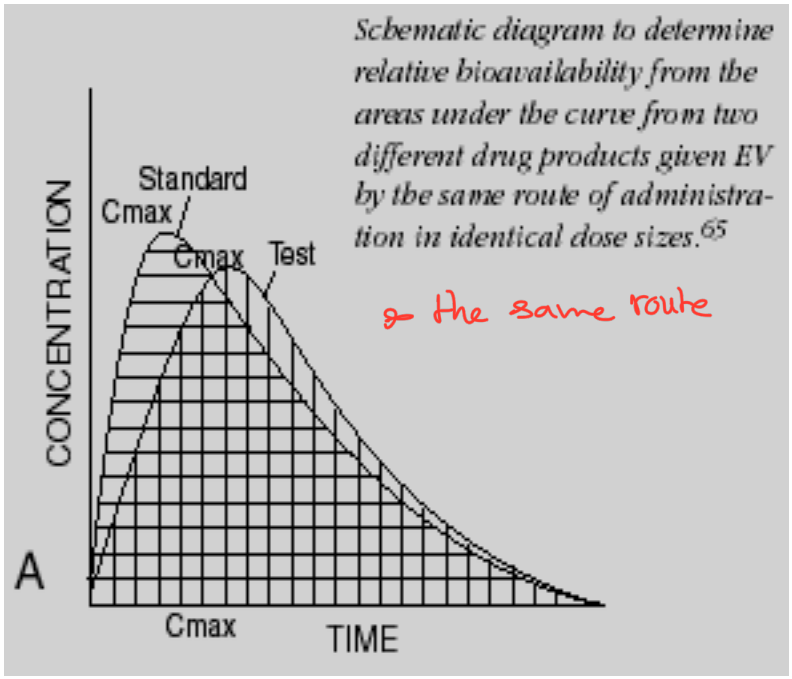
$$F = \frac{[AUC]_{po} * dose_{IV}}{[AUC]_{IV} * dose_{po}}$$



Relative Bioavailability

- **The relative bioavailability** is the systemic availability of a drug from one drug product (*A*) compared to another drug product (*B*) as Capsule Vs Tablet. (other than IV)

$$relative\ bioavailability = \frac{[AUC]_A * dose_B}{[AUC]_B * dose_A}$$

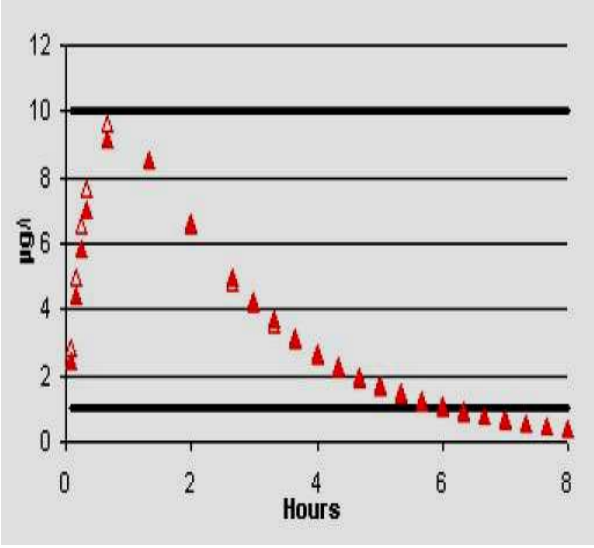


Bioavailability and Bioequivalence

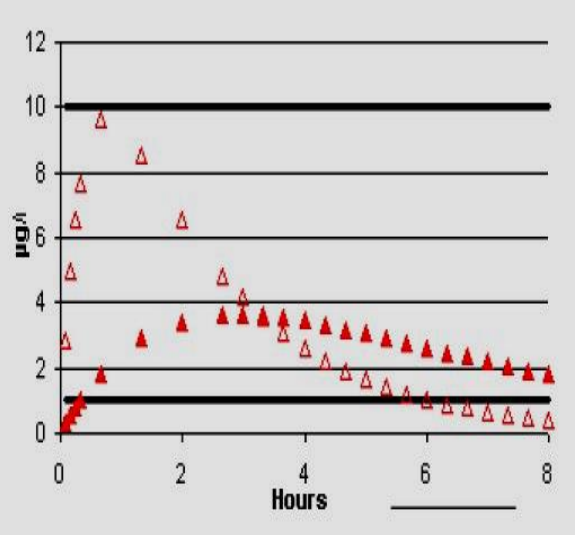
Bioequivalence:

- means pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the **same molar dose** of the therapeutic moiety under similar experimental conditions.
- Bioequivalence studies are usually performed to compare the rate and/or extent of absorption of a new drug product or a generic equivalent with that of a recognized standard (usually original).

Two dosage forms are bioequivalent



Two dosage forms are not bioequivalent



Bioavailability and Bioequivalence

البدائل الصيدلانية

- **Pharmaceutical Alternatives:**

  means 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**.

المتكافئة

- **Pharmaceutical Equivalent:**

  means drug products that contain **identical amounts** of the identical active drug ingredient, i.e., **the salt or ester of the same therapeutic moiety**, in **identical dosage forms**, but **not** necessarily containing the same **inactive ingredients**, and that meet the identical applicable standard of identity, strength, quality, and purity, including potency and where applicable, content uniformity, disintegration times and/or dissolution rate.

Bioavailability and Bioequivalence

- **Brand Name:** is the trade name of the drug.
- **Chemical Name:** is the name used by the organic chemist to indicate the chemical structure of the drug.
- **Generic Name:** is the established, non proprietary or common name of the active drug in a drug product.

Methods to Assess Bioavailability:

1. **Dissolution at administration or absorption site**:

Method of evaluation: Dissolution rate

Example: *In vitro:* water, buffer, artificial gastric fluid, artificial intestinal fluid, artificial saliva, artificial rectal fluid.

Bioavailability and Bioequivalence

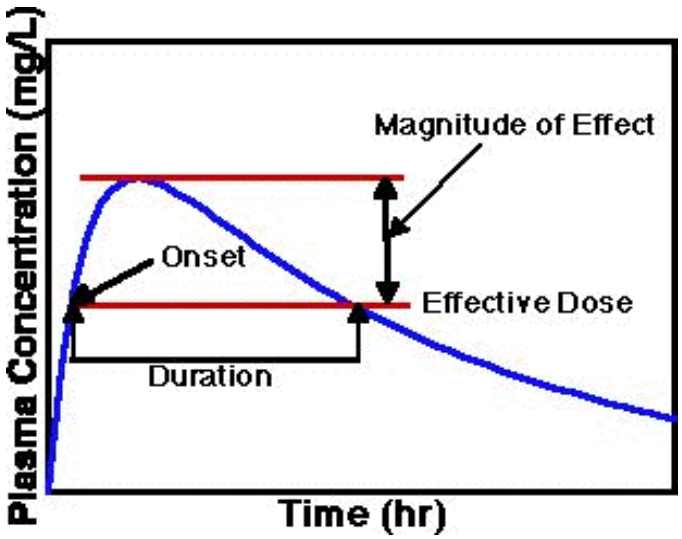
II. Free drug in systemic circulation:

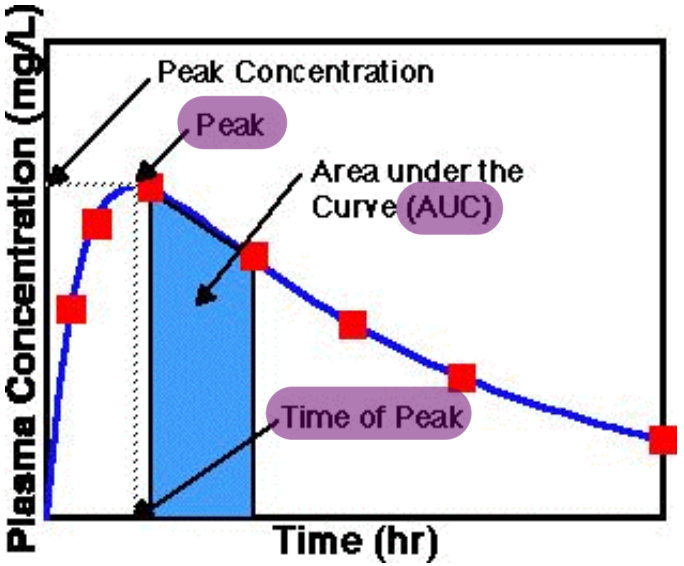
Method of evaluation:

1. Blood level time profile
2. Peak blood level
3. Time to reach peak
4. Area under blood level time curve

Example: *In vivo:* whole blood, plasma, serum

داخل الجسم





Bioavailability and Bioequivalence

III. Pharmacologic effect:

Method of evaluation: onset of effect, duration of effect , and intensity of effect

Example: *In vivo:* discriminate measurement of pharmacologic effect (blood pressure, blood sugar, blood coagulation time)

IV. Clinical response:

Method of evaluation: controlled clinical blind or double- blind study, observed clinical success or failure

Example: *In vivo:* evaluation of clinical responses

V. Elimination:

Method of evaluation: cumulative amount of drug excreted, maximum excretion rate and peak time of excretion.

Example: *In vivo:* urine

Practice Problem

- The bioavailability of a new 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 200 mg of the drug. The average AUC values are given in the table below. From these data, calculate:

Drug Product	Dose (mg)	AUC (ug. hr/mL)
Oral tablet	200	50
Oral solution	200	75
IV bolus injection	200	150

  - the relative bioavailability of the drug from the tablet compared to the oral solution
  - the absolute bioavailability of the drug from the tablet.

Factors Affecting Bioavailability

1. **Gastric emptying:** Although not true in all cases, increased gastric emptying generally enhances bioavailability of orally administered drugs. Gastric emptying depends on the following factors:
   - Volume of liquid intake
   - Volume of solid food intake and its fat content
   - Viscosity of stomach content
   - pH of the stomach
   - Intake of other drugs
   - Age and weight of the patients
   - Physical activity of the patients taking drug
   - Emotional state of the patient
   - Various disease states

Factors Affecting Bioavailability

→ First pass

2. Pre-systemic and systemic metabolism decrease bioavailability.

Pre-systemic metabolism, which occurs during first-pass metabolism, can decrease the bioavailability of a drug. The following types of metabolism are commonly seen:

- First-pass metabolism occurs when an absorbed drug passes directly through the liver before reaching systemic circulation after oral administration.
- Intestinal metabolism: Drug metabolizes in the intestine itself or during the passage through the intestinal wall.
- Hydrolysis of the drug in the stomach fluids.
- Transporters such as p-glycoprotein may influence the bioavailability of a drug.

Factors Affecting Bioavailability

3. Complexation with other agents in the gastrointestinal tract

4. Formulation factors, such as may occur with inert ingredients, the manufacturing process and/or use of surfactants, etc.

bioavailability ← تحسن الـ