Drug excretion (Cont.):

Renal clearance is then:-

$$CL_{renal} = \frac{\text{filtration rate} + \text{secretion rate} - \text{reabsorption rate}}{Cp}$$

$$\text{Renal Clearance} = \frac{\text{Rate of Excretion}}{\text{Plasma Concentration}}$$

Factors Altering Renal Drug Clearance:

Renal drug clearance is lower [therefore you must reduce dose] in:

- Elderly and Newborn
- Women (20%) than men
- Kidney and Heart Disease
- Patients taking drugs which block secretion (aspirin,probenecid)

Drug excretion (Cont.):

Hemodialysis:

- Hemodialysis or `artificial kidney' therapy is used in renal failure to remove toxic waste material normally removed by the kidneys.

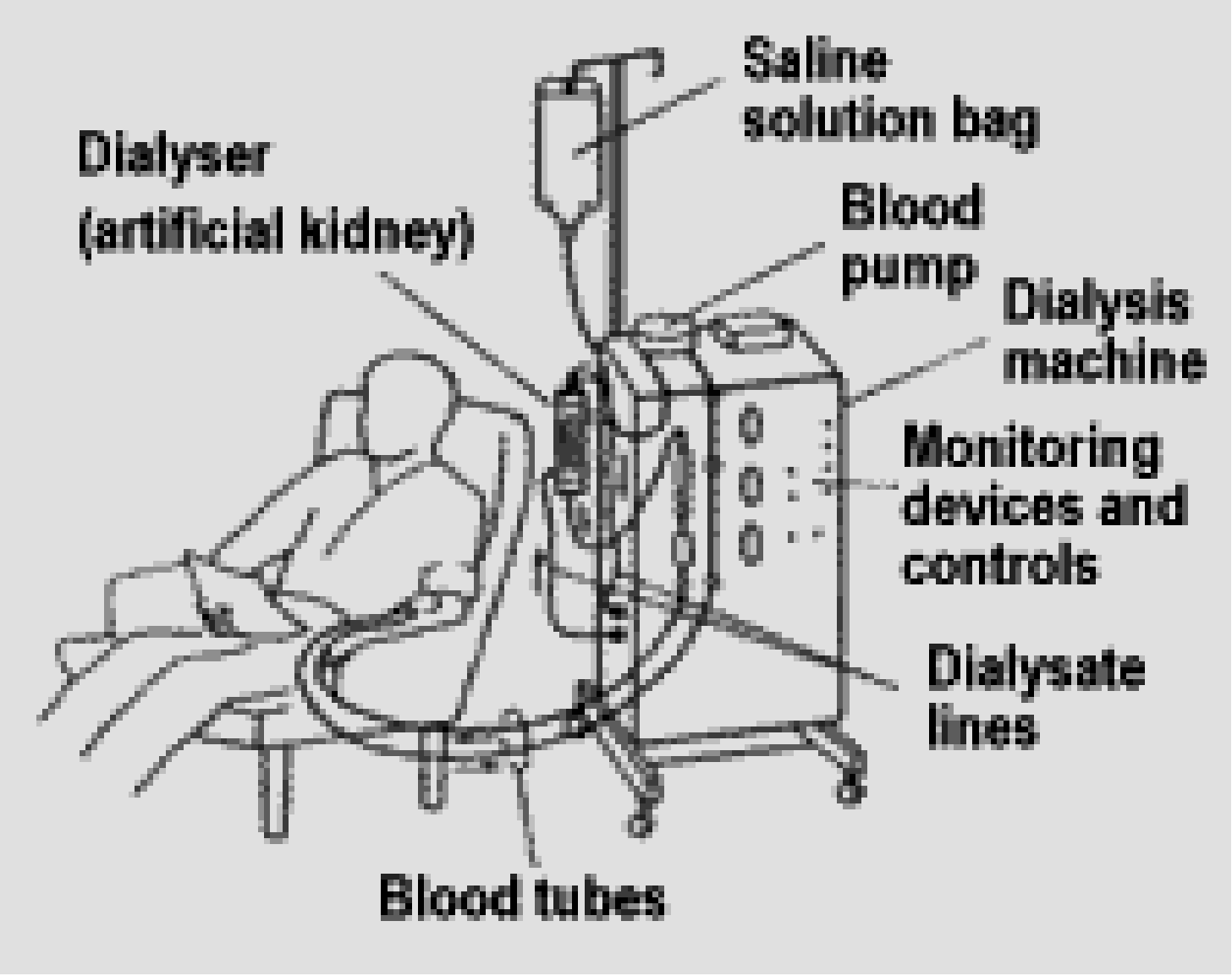
- In the procedure blood is diverted externally and allowed to flow across a semi-permeable membrane that is bathed with an aqueous isotonic solution. Nitrogenous waste products and some drugs will diffuse from the blood, thus these compounds will be eliminated.

- This technique is particularly important with drugs which:-

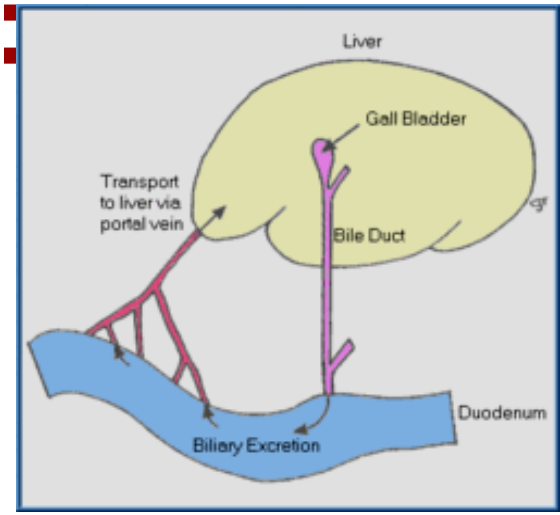
1) have good water solubility;
2) are not tightly bound to plasma protein;
3) are smaller molecular weight; and
4) have a small apparent volume of distribution.

- Drugs which are tightly bound or extensively stored or distributed into tissues are poorly removed by this process.

Haemodialysis



Drug excretion (Cont.):



2.Fecal excretion:

Elimination of toxicants in the feces occurs from two processes:

A- excretion in bile:

- Some heavy metals are excreted in the bile, e.g., arsenic, lead, and mercury. However, the most likely substances to be excreted via the bile are comparatively large, ionized molecules, such as large molecular weight (greater than 300) conjugates e.g. morphine and chloramphenicol (as glucuronide).

- The biliary secretion is active since bile/plasma concentrations maybe as high as 50/1. There can also be competition between compounds.

Drug excretion (Cont.):

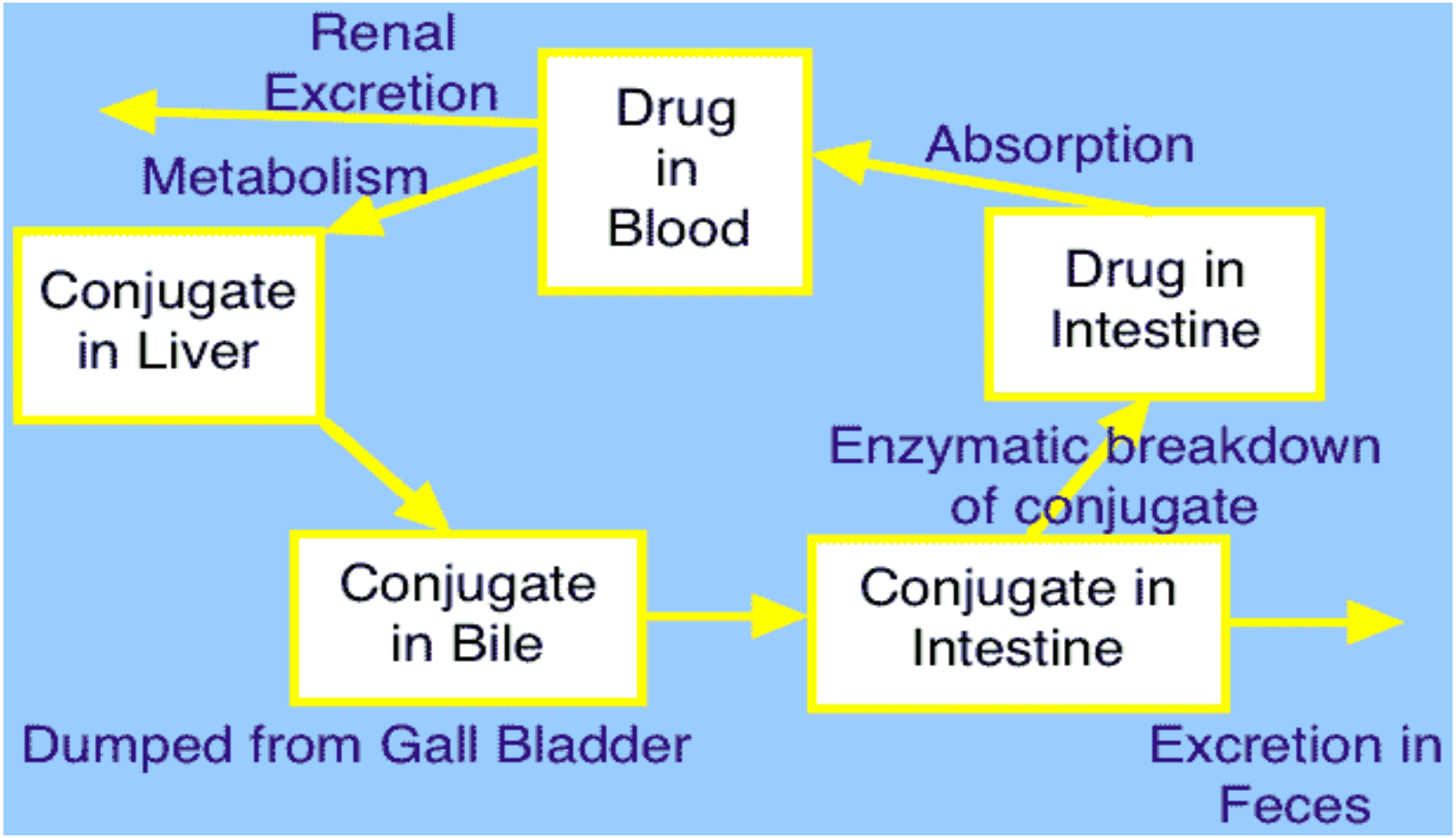
- Once a substance has been excreted by the liver into the bile, and subsequently into the intestinal tract, it can then be eliminated from the body in the feces, or it may be reabsorbed.

- Since most of the substances excreted in the bile are water-soluble, they are not likely to be reabsorbed as such. However, enzymes in the intestinal flora are capable of hydrolyzing some glucuronide and sulfate conjugates, which can release the less-polar compounds that may then be reabsorbed. This process is known as the **enterohepatic circulation.**

- The effect of this enterohepatic circulation is to prolong the life of the drug in the body.

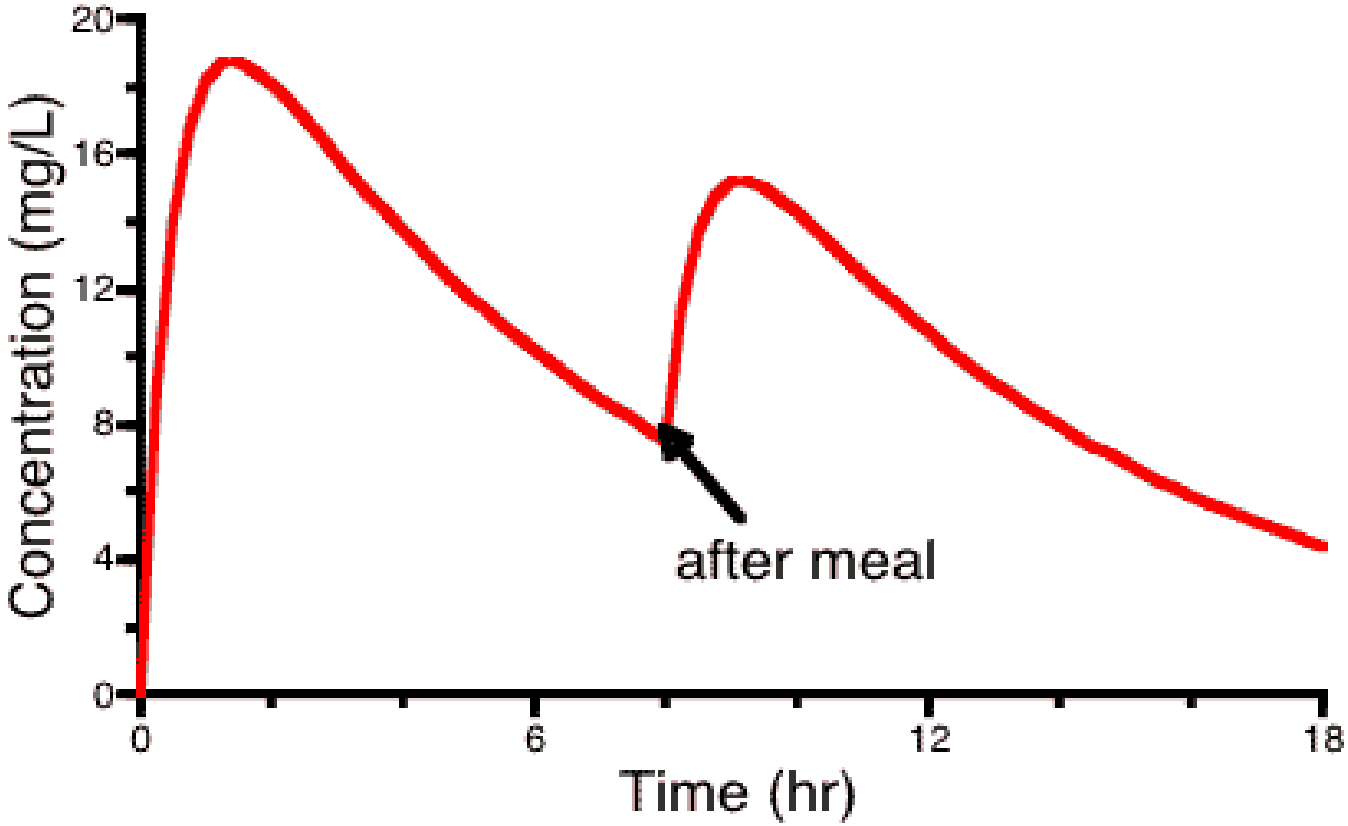
Drug excretion (Cont.):

Enteroheptic Recycling



Drug excretion (Cont.):

Cp versus Time showing a Second Peak



Drug excretion (Cont.):

- Another way that drugs can be eliminated via the feces is by:

B- direct intestinal excretion:

- Orally administered drugs may be excreted in the feces if they are incompletely absorbed or not absorbed at all (e.g. Cholestyramine)

- Increasing the lipid content of the intestinal tract can enhance intestinal excretion of some lipophilic substances. For this reason, mineral oil is sometimes added to the diet to help eliminate toxic substances, which are known to be excreted directly into the intestinal tract.

Drug excretion (Cont.):

Drugs may be excreted by passive diffusion from:

3. Pulmonary excretion:

- The lung is the major organ of excretion for gaseous and volatile substances. Most of the gaseous anesthetics are extensively eliminated in expired air.

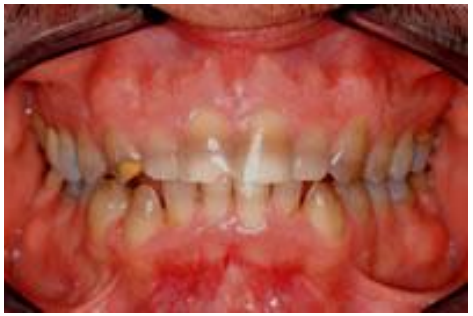
4. Salivary excretion:

- Drug excretion into saliva appears to be dependent on pH partition and protein binding.
- In some instances, salivary secretion is responsible for localized side effects. For example, excretion of antibiotics may cause black hairy tongue, and gingival hyperplasia can be a side effect of phenytoin.

Drug excretion (Cont.):

Examples of compounds that excreted in saliva:

- Neonatal jundice result from sulfonamide interaction with bilirubin.
- Superinfection from antibiotics.
- Dental mottling upon tetracycline ingestion.

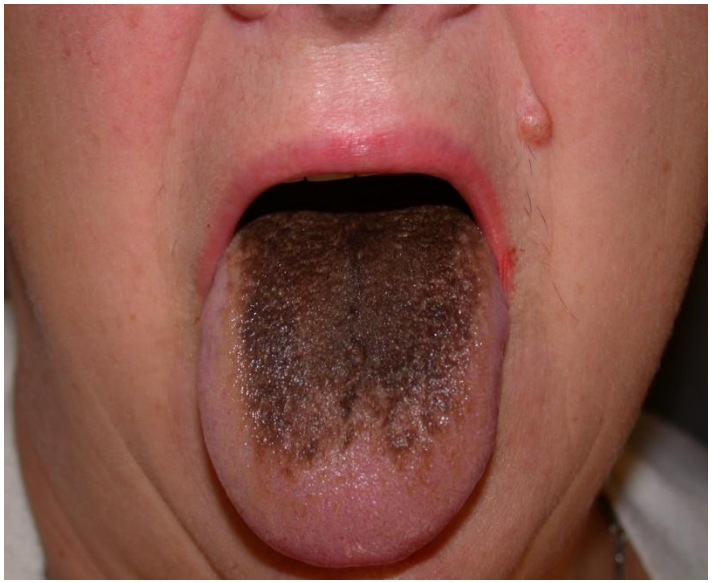


- Mothers smoking more than 20 to 30 cigarettes a day may induce nausea, vomiting, abdominal cramps and diarrhea in the infant.

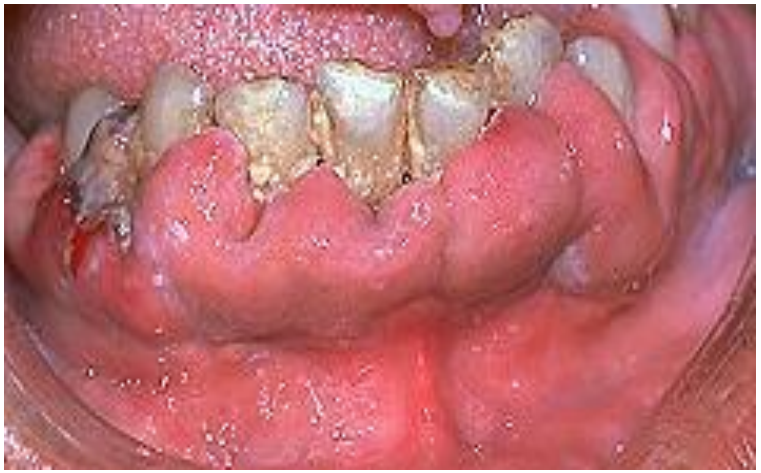
5. Skin excretion:

- Iodine, bromine, benzoic acid, salicylic acid, lead, arsenic mercury , iron and alcohol are examples of compounds that excreted in sweat.

Black hairy tongue



gingival hyperplasia



Drug excretion (Cont.):

6. Mammary excretion:

Both a-basic substances and b-lipid-soluble compounds can be excreted into milk.

Basic substances can be concentrated in milk since milk is more acidic (pH ~ 6.5) than blood plasma.

Since milk contains 3-4% lipids, lipid-soluble drugs can diffuse along with fats from plasma into the mammary gland and thus can be present in mother's milk.

C-Substances that are chemically similar to calcium can also be excreted into milk along with calcium.

D-Ethanol and tetracycline enter the milk by diffusion through membrane pores (of mammary alveolar cells).

Bioavailability and Bioequivalence:

Bioavailability:

It is a measurement of the extent of a therapeutically active drug that reaches the systemic circulation and is available at the site of action.

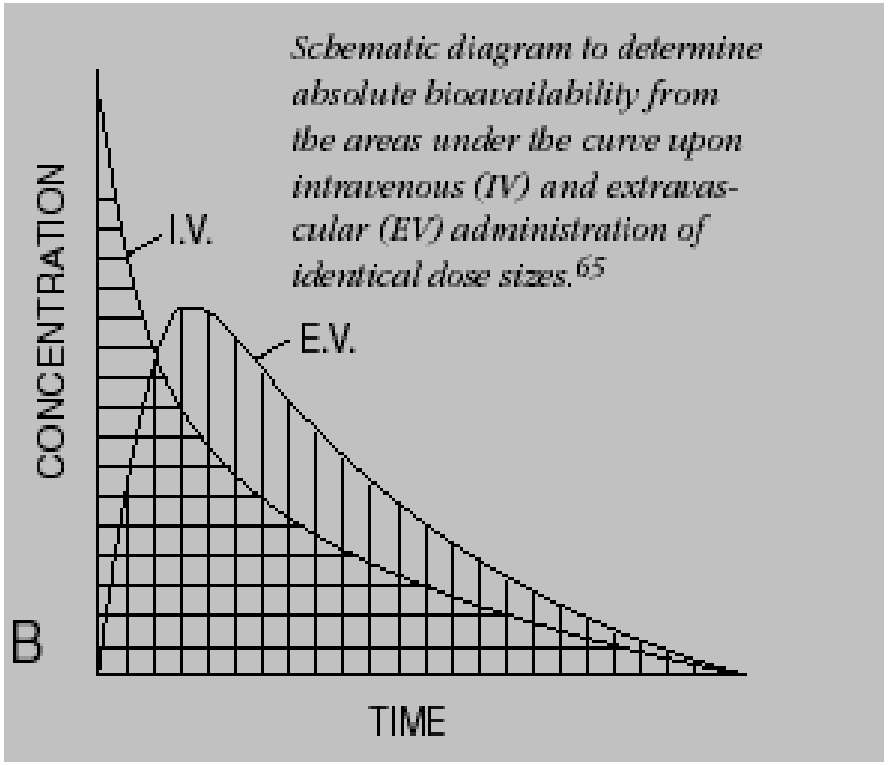
Absolute bioavailability:

Absolute bioavailability compares the bioavailability (estimated as area under the curve, or AUC) of the active drug in systemic circulation following non-intravenous administration (i.e., after oral, rectal, transdermal, subcutaneous administration), with the bioavailability of the same drug following intravenous administration.

Bioavailability and Bioequivalence:

It is the fraction of the drug absorbed through non-intravenous administration compared with the corresponding intravenous administration of the same drug.

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

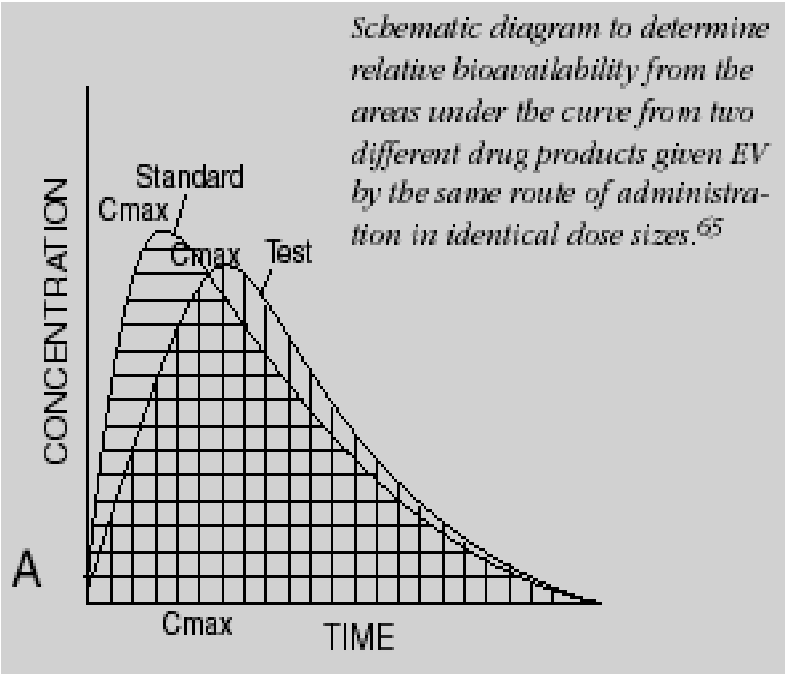


Bioavailability and Bioequivalence:

Relative bioavailability:

This measures the bioavailability (estimated as area under the curve, or AUC) of a certain drug when compared with another formulation of the same drug, usually an established standard, or through administration via a different route.

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



Bioavailability and Bioequivalence:

Bioequivalence:

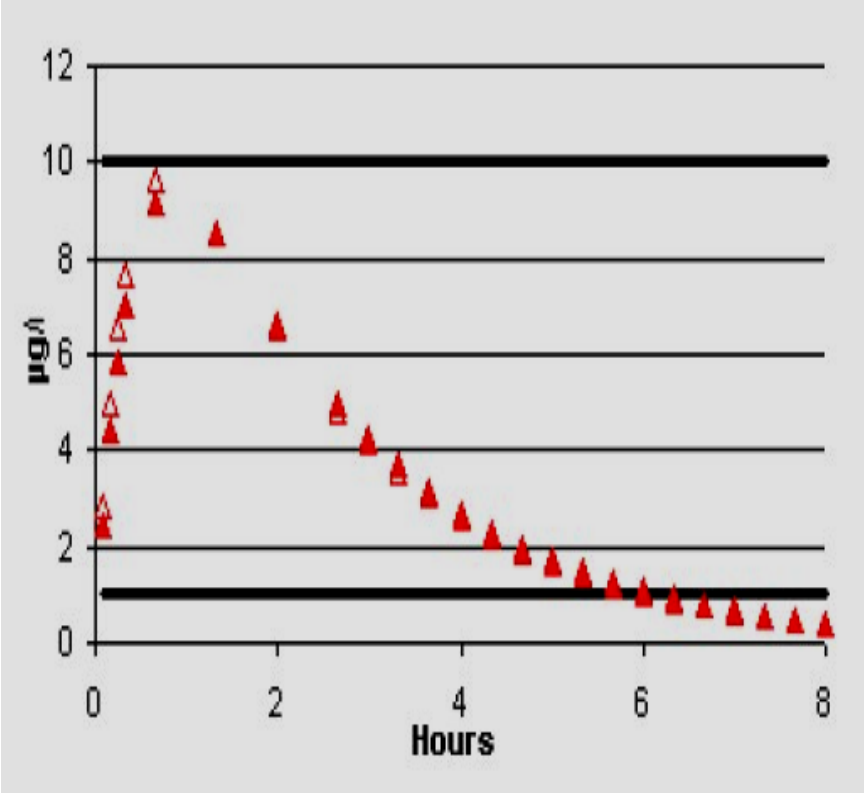
- means pharmaceutical equivalents or pharmaceutical alternatives whose rate and extent of absorption do not show a significant difference when administered at the same molar dose of the therapeutic moiety under similar experimental conditions.

- 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.

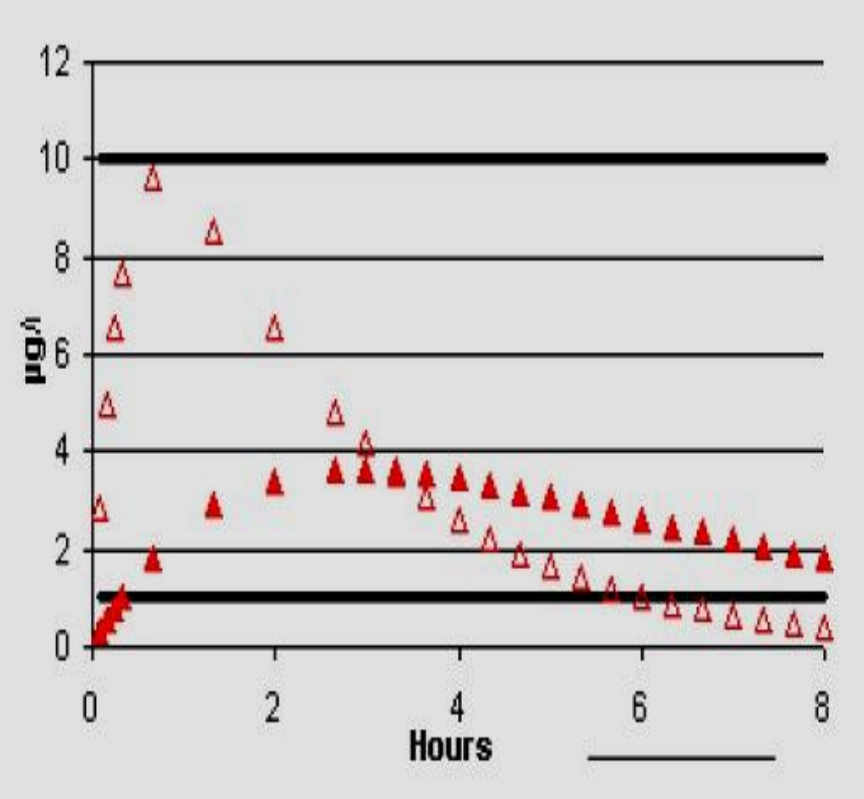
-

Bioavailability and Bioequivalence:

Two dosage forms are bioequivalent:



Two dosage forms are not bioequivalent:



Bioavailability and Bioequivalence:

- **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.

- **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 compendial or other applicable standard of identity, strength, quality, and purity, including potency and where applicable, content uniformity, disintegration times and/or dissolution rate.

- **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.

Bioavailability and Bioequivalence:

Methods to Assess Bioavailability:

I. Dissolution at administration or absorption site:

Method of evaluation: Dissolution rate

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

II.Free drug in systemic circulation:

Method of evaluation: 1.Blood level time profile

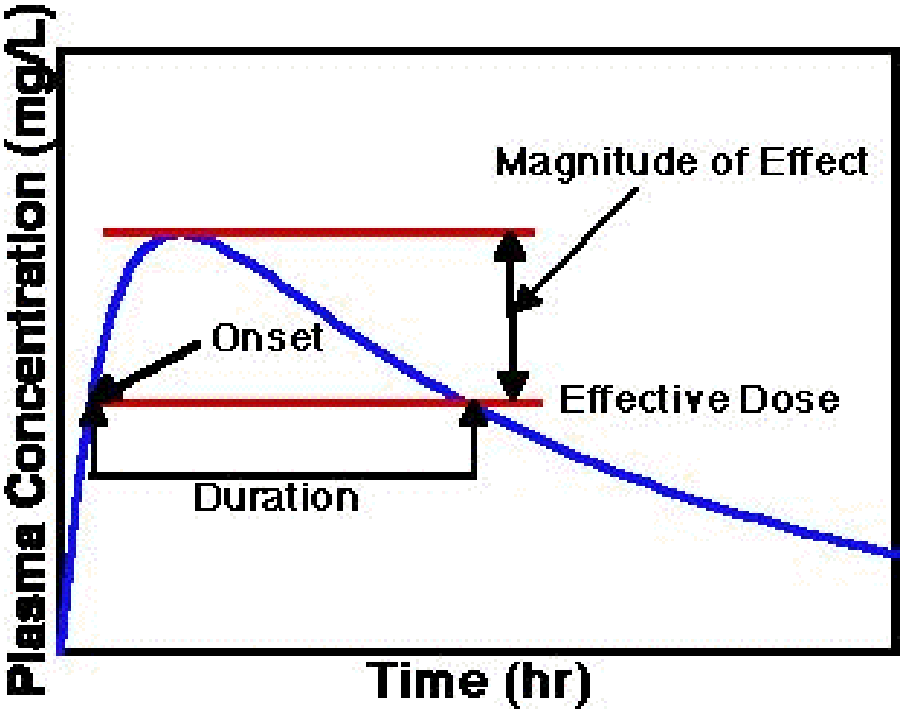
2.Peak blood level

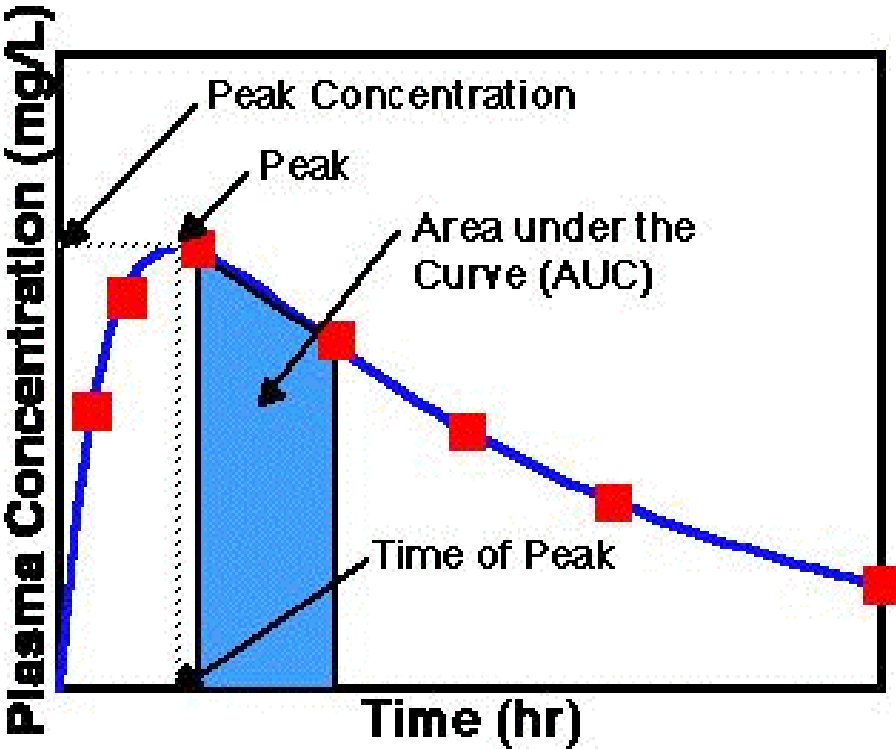
3.Time to reach peak

4.Area under blood level time curve

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

Introduction to bipharmaceutics (Cont.):





Bioavailability and Bioequivalence:

III. Pharmacologic effect:

Method of evaluation: 1.Onset of effect

2.Duration of effect

3.Intensity of effect

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

IV. Clinical response:

Method of evaluation: 1.Controlled clinical blind or double-blind study

2.Observed clinical success or failure

Example: *In vivo:* evaluation of clinical responses

Bioavailability and Bioequivalence:

V. Elimination:

Method of evaluation: 1.Cumulative amount of drug excreted

2.Maximum excretion rate

3.Peak time of excretion

Example: *In vivo:* urine