Bioavailability

- **Bioavailability:**
- “The relative amount of an administered dose that reaches the general circulation and the rate at which this occurs” (American Pharmaceutical Association, 1972).

- “The rate and extent to which the active ingredient or therapeutic moiety is absorbed from a product and becomes available at the site of drug action” (US Food and Drug Administration,1977).

- **Objectives of bioavailability studies:**
- Development of new formulations.
- Determination of influence of excipients, patient related factors and possible interaction with other drugs on the efficiency of absorption.
- Control of quality of a drug product during the early stages of marketing in order to determine the influence of processing factors, storage, stability on drug absorption.
- Primary stages of the development of a suitable dosage form for a new drug entity.
- Useful in determining the safety and efficacy of the drug product.
- To find out the influence of physicochemical properties of drug and dosage form on biological performance of the drug.

- **Bioavailability data are used to determine:**

1. The amount or proportion of drug absorbed from a formulation or dosage form.
2. The rate at which the drug was absorbed.
3. The duration of the drug's presence in the biologic fluids or tissue and when correlated with patient response.
4. The relationship between drug blood levels and clinical efficacy and toxicity.
5. To compare the availability of drug substance from different dosage form or from the same dosage form produced by different manufactures.

- **Types of Bioavailability:**
  1. Absolute Bioavailability.
  2. Comparative (or relative) Bioavailability.

  - ***Absolute Bioavailability:*** the fraction of administered dose which reaches systemic circulation = F.

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

- ➢ **From area under the plasma concentration–time curve data:**
  - Absolute bioavailability (extent)=fraction of drug absorbed (F)

$$F = \frac{(AUC)_0^{\infty}\ extravascular}{(AUC)_0^{\infty}\ IV}$$ for administration of the same dose to the same individual

$$F = \frac{\frac{(AUC)_0^{\infty}\ extravascular}{Dose\ \ extravascular}}{\frac{(AUC)_0^{\infty}\ IV}{Dose\ \ IV}}$$

Or

$$\mathbf{F} = \frac{(AUC)_0^{\infty} oral}{(AUC)_0^{\infty}\ IV} \times \frac{Dose\ Iv}{Dose\ oral}$$

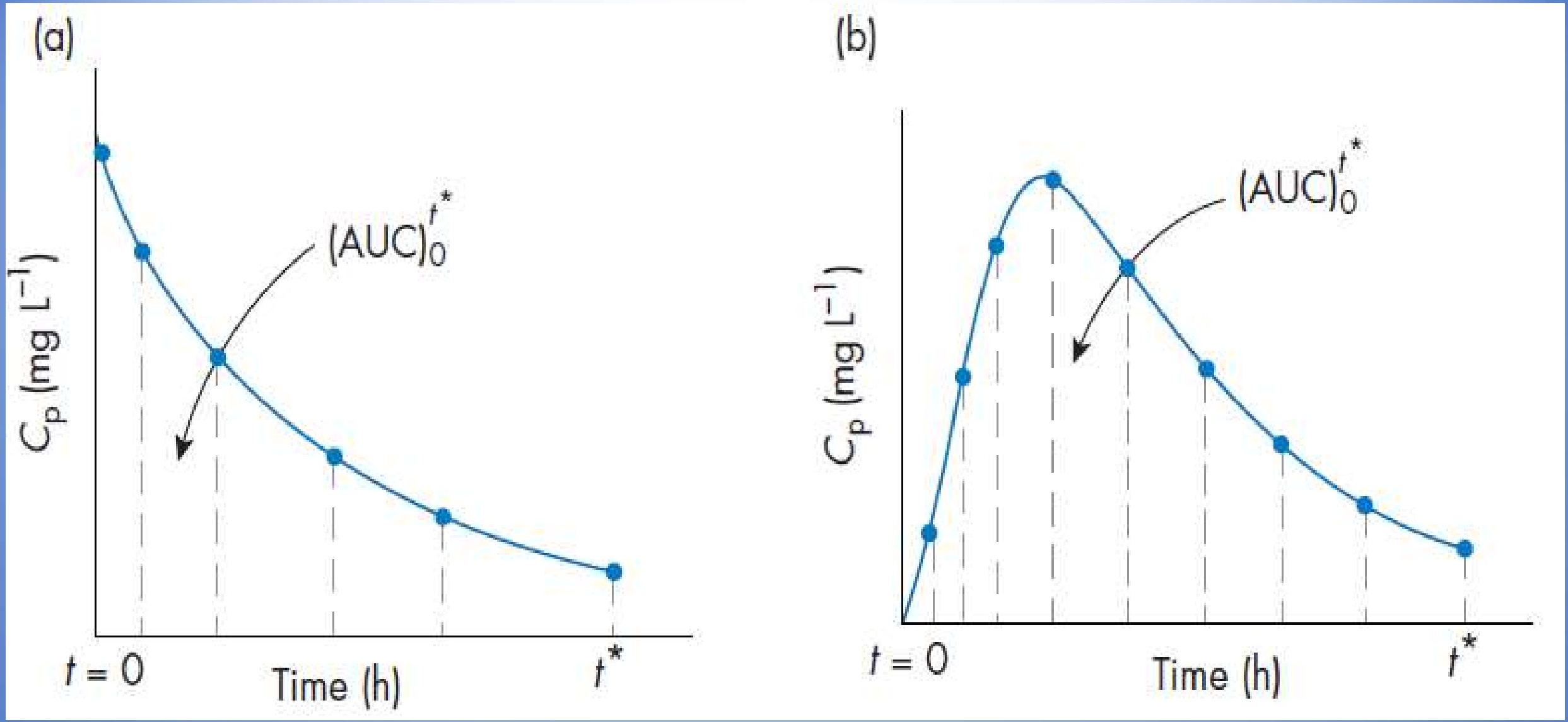


Fig .Plasma concentration (Cp) versus time data following the administration of a dose of a drug as an IV bolus (a) or by an extravascular route (b).

$[(AUC)_0^*$, area under the plasma concentration versus time curve from time zero to t*].

- ➢ **From urinary data:**

$$F = \frac{\frac{Xu^{\infty}\ extravascular}{Dose\ \ extravascular}}{\frac{Xu^{\infty}\ IV}{Dose\ IV}}$$

Or

$$F = \frac{Xu^{\infty}\ oral}{Xu^{\infty}\ IV} \times \frac{Dose\ Iv}{Dose\ oral}$$

F= 1 For drug given IV

F≤ 1 For extravascular route

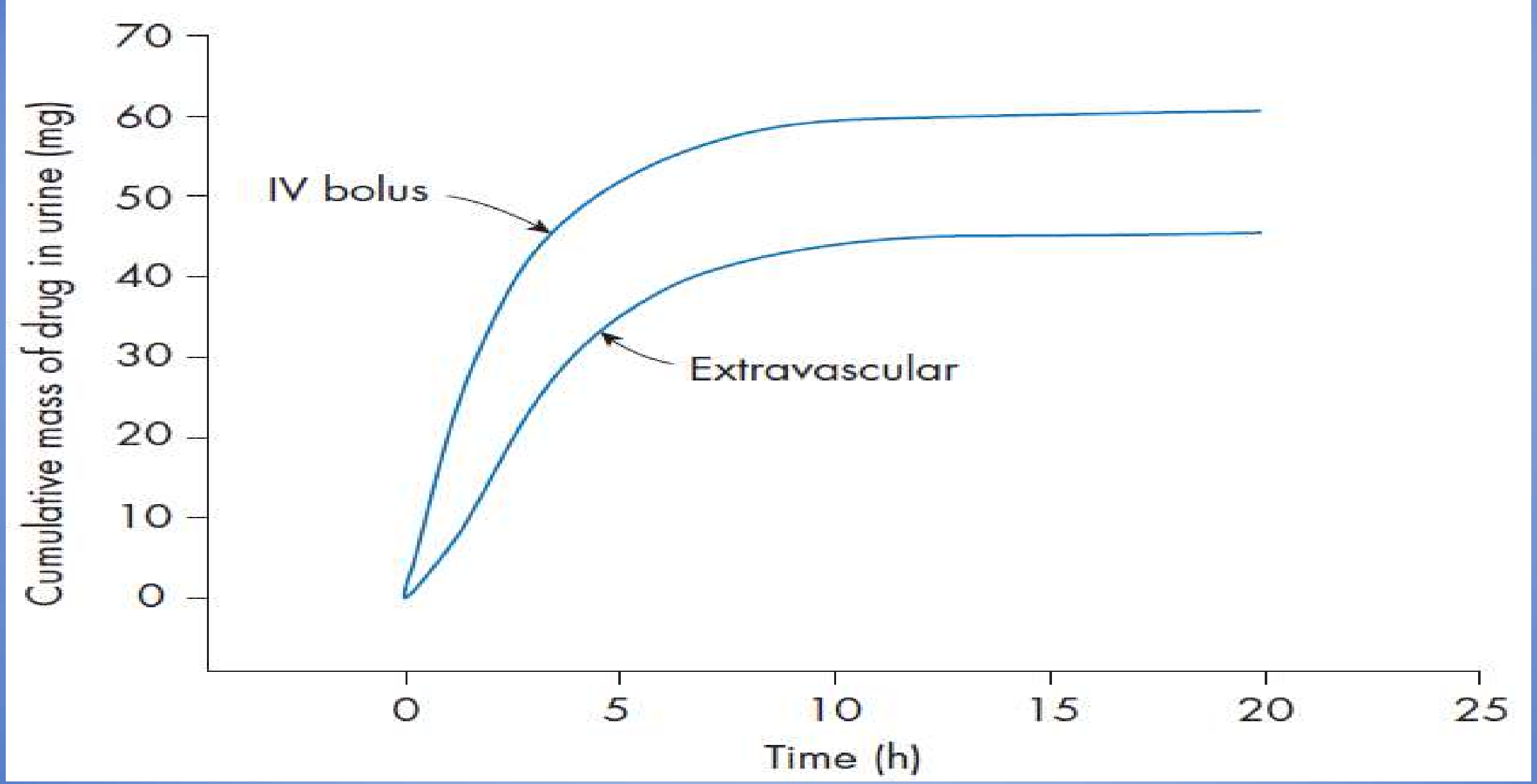


Fig. A plot of cumulative amount of drug eliminated in urine following the administration of a dose of a drug as an (IV) bolus and by an extravascular route.

- ***Comparative (or relative) Bioavailability:***

Is the bioavailability of a drug product as compared to a recognized standard for the same doses.

- **From area under the plasma concentration–time curve data:**

$$F_{rel} = \frac{(AUC_0^{\infty})_{tablet}}{(AUC_0^{\infty})_{solution}} \times \frac{Dose_{solution}}{Dose_{tablet}}$$

$$F_{rel} = \frac{(AUC_0^{\infty})_{IM}}{(AUC_0^{\infty})_{oral}} \times \frac{Dose_{oral}}{Dose_{IM}}$$

When plasma concentration data are utilized in the determination of the comparative (or relative) bioavailability, please note that (Cp)max and (tmax) for the test and the reference products, in addition to the relative fraction of drug absorbed must also be compared.

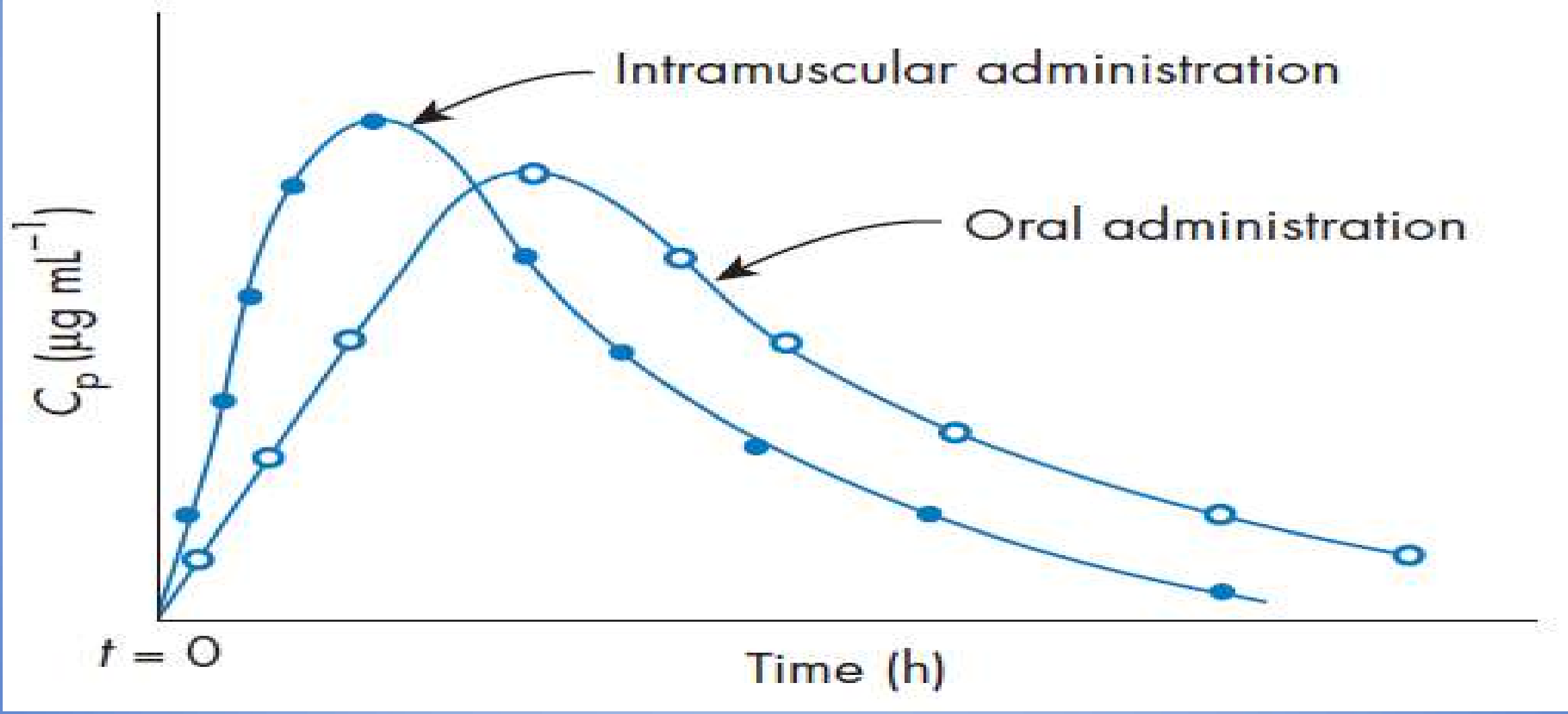


Fig. A plot of plasma concentration (Cp) versus time data following the administration of the dose of a drug by two different extravascular routes (or this could be via two different dosage forms and the same extravascular route or two different formulations).

- **➢From urinary data:**

$$\text{F rel (\%R.B)} = \frac{Xu^{\infty}\ A}{Xu^{\infty}\ B} \cdot 100$$

Unlike absolute bioavailability, the comparative (relative) bioavailability of a drug can be >1, <1 or 1.

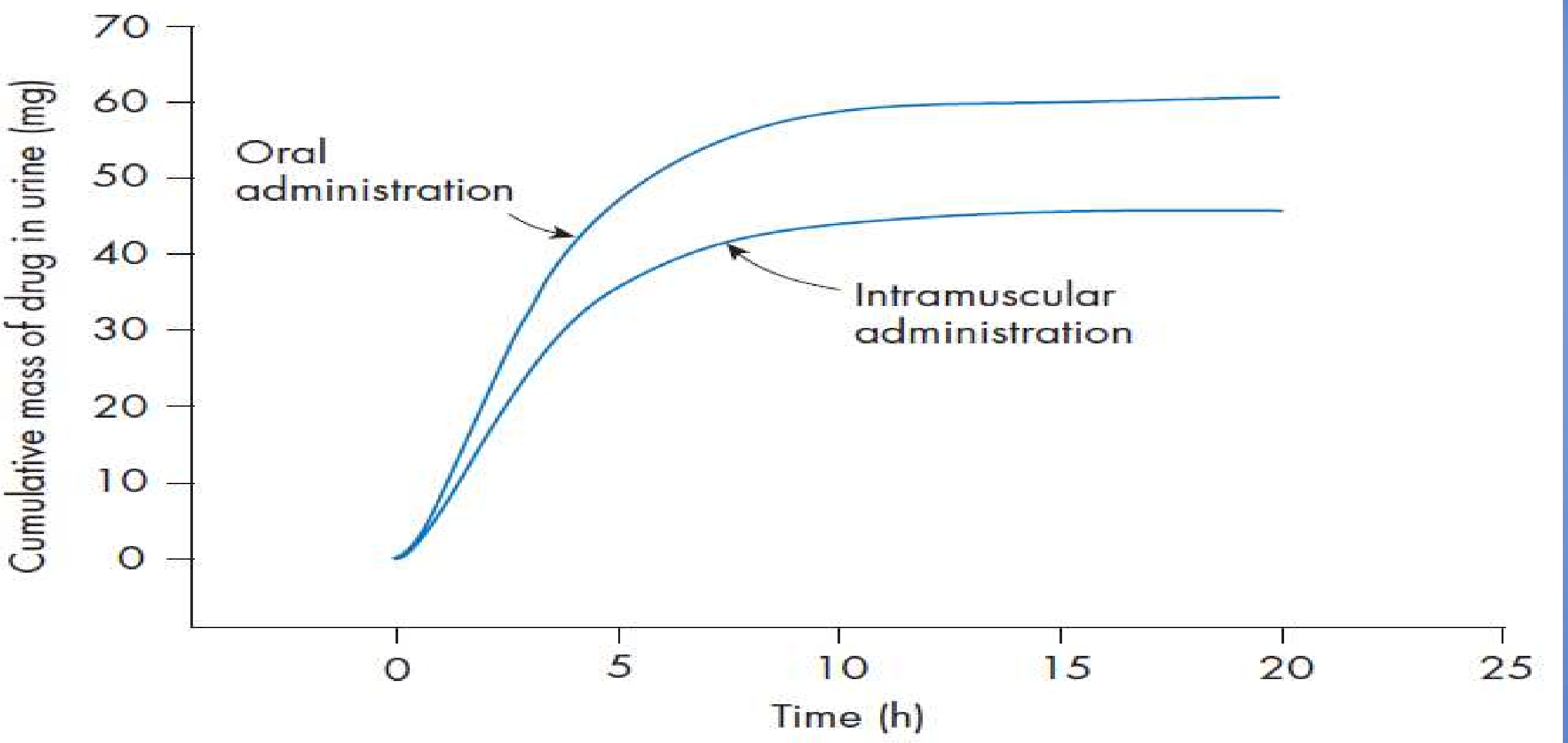


Fig. A plot of cumulative amount of drug eliminated in urine following the administration of a drug by two different extravascular routes (or this could be via two different dosage forms and same extravascular route, or two different formulations and same dosage form).

Bioequivalence

- Bioequivalence is a type of comparative or relative bioavailability study. However, in a bioequivalence study, $(AUC)_0^\infty$, peak plasma concentration and peak time are determined for two or more chemically or pharmaceutically equivalent products (identical dosage forms) where at least one of them is an innovator product (also known as the Brand Name or Reference Standard)
- The parameters evaluated in a bioequivalency study are $(AUC)_0^\infty$, peak plasma concentrations and peak time.

$$F_{rel} = \frac{(AUC)_0^\infty}{(AUC)_0^\infty} \times \frac{Dose_{standard}}{Dose_{generic}}$$

- **Methods for Assessing Bioavailability:**

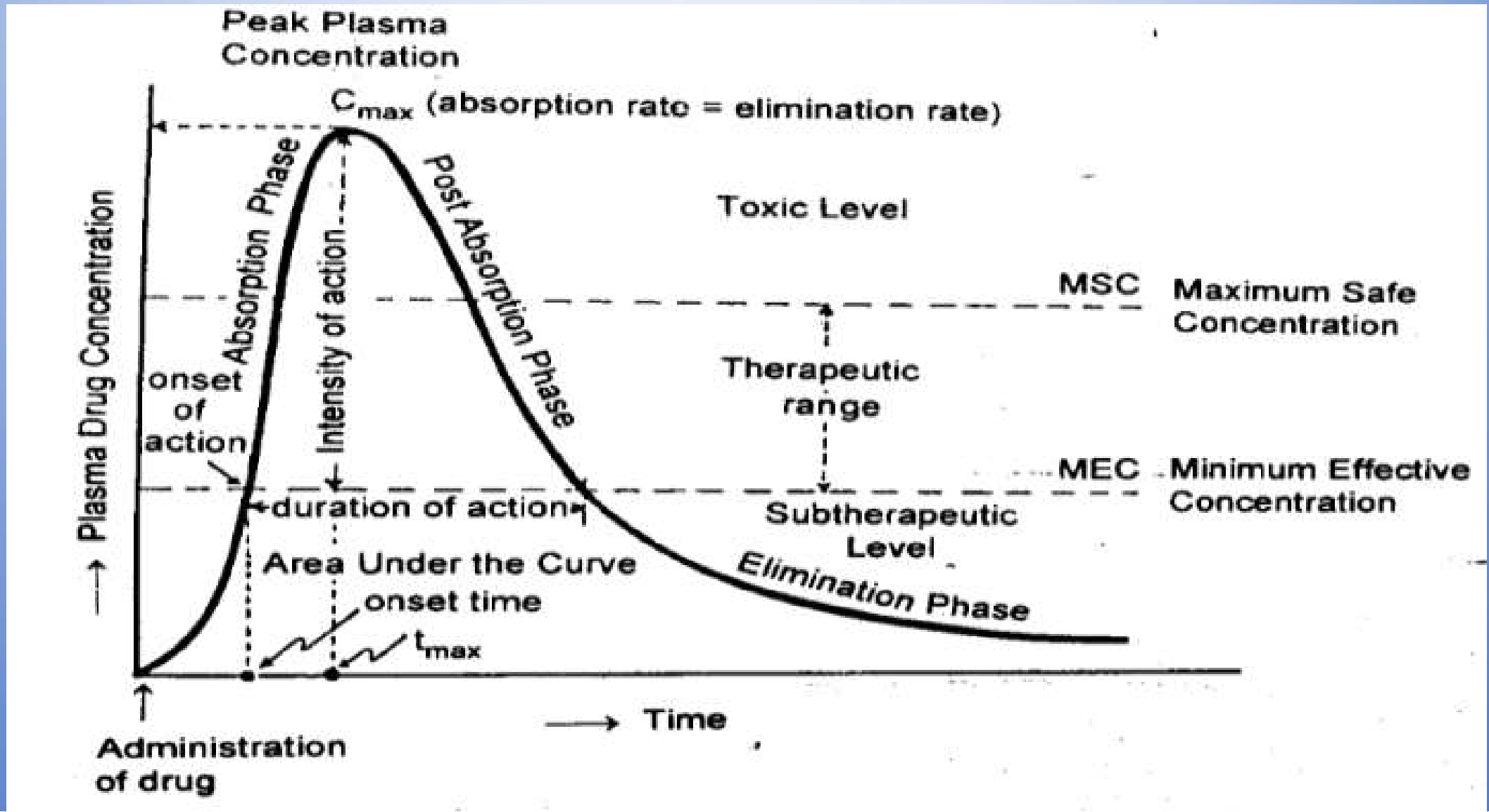
There are several direct and indirect methods of assessing Bioavailability in humans. The selection of method depends on the purpose o the study, the analytical method of drug measurement, and the nature of the drug product.

I- Assessment of bioavailability from plasma data

II-Assessment of bioavailability from urine data

III-Assessment of bioavailability using Acute Pharmacological Effect

I- Assessment of bioavailability from plasma data



- ***I- Assessment of bioavailability from plasma data :***

Using:

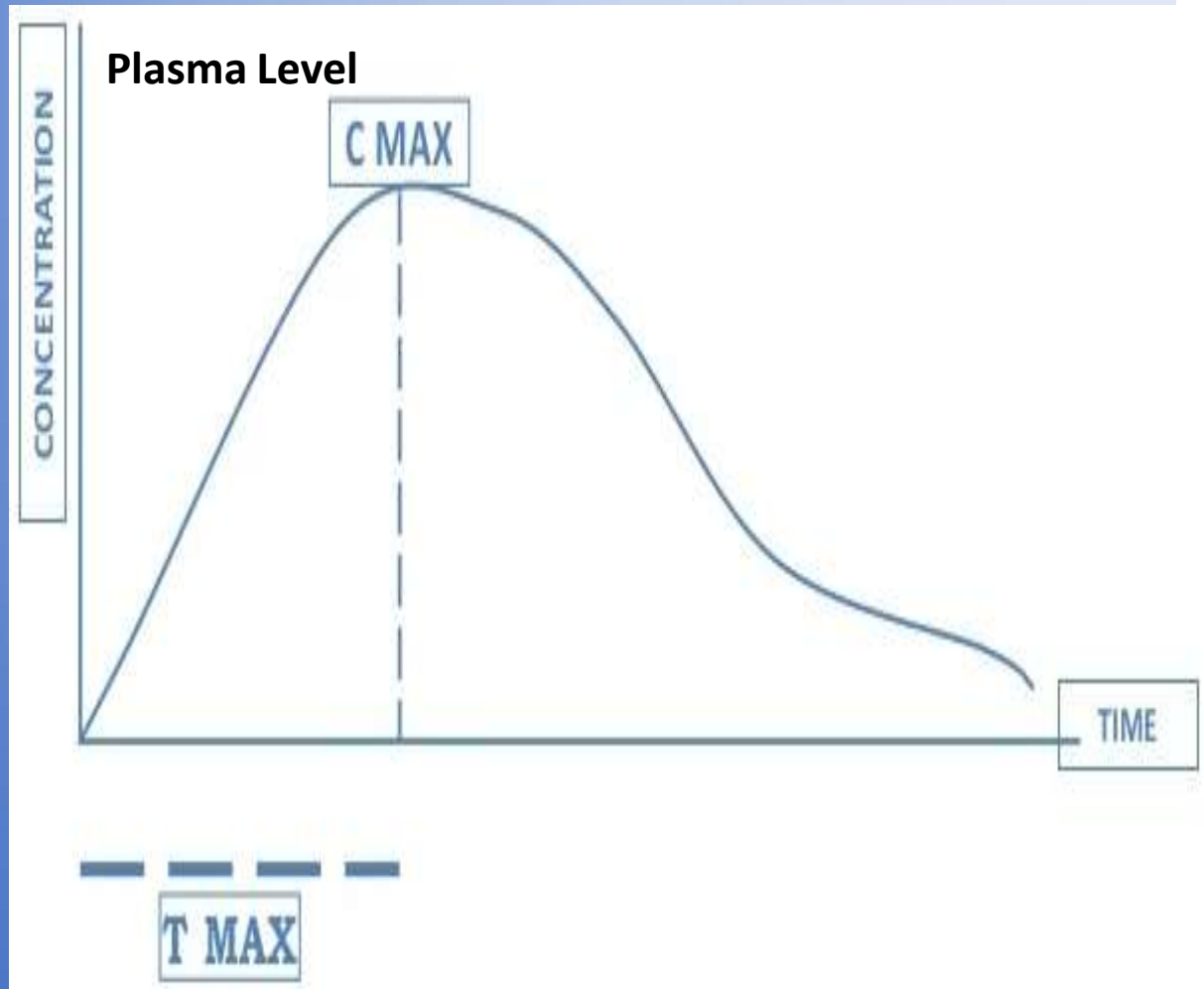
1- Tmax : $$tmax = ln \frac{Ka}{Ke} \times \frac{1}{Ka-ke} = log \frac{Ka}{Ke} \times \frac{2.303}{Ka-Ke}$$

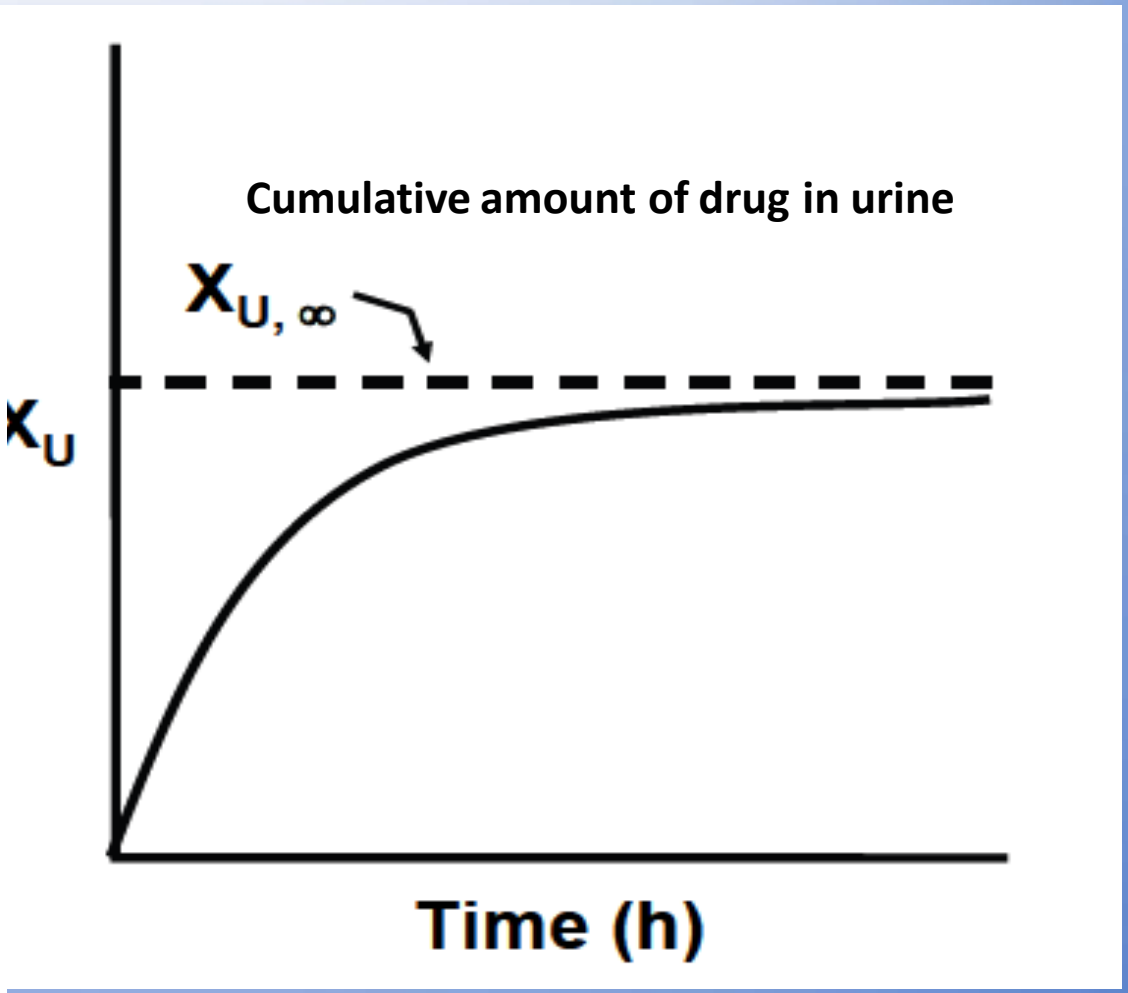
2- Cmax: $$Cmax = Ao \cdot \frac{Ka}{ka-Ke} (e^{-Ke.tmax} - e^{-Ka.tmax})$$

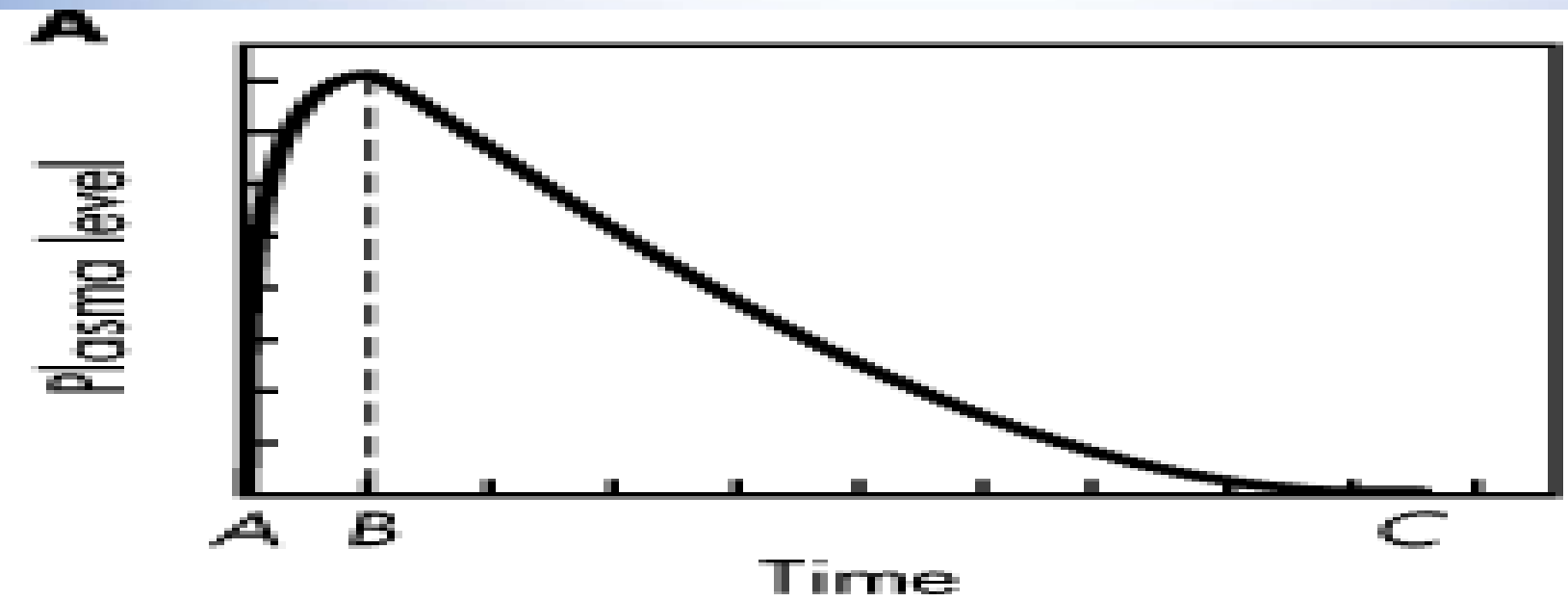
3- $$(AUC)_0^\infty = \frac{FXo}{Vd.Ke} = \frac{FXo}{Cl} = \frac{Ao}{Ke}$$

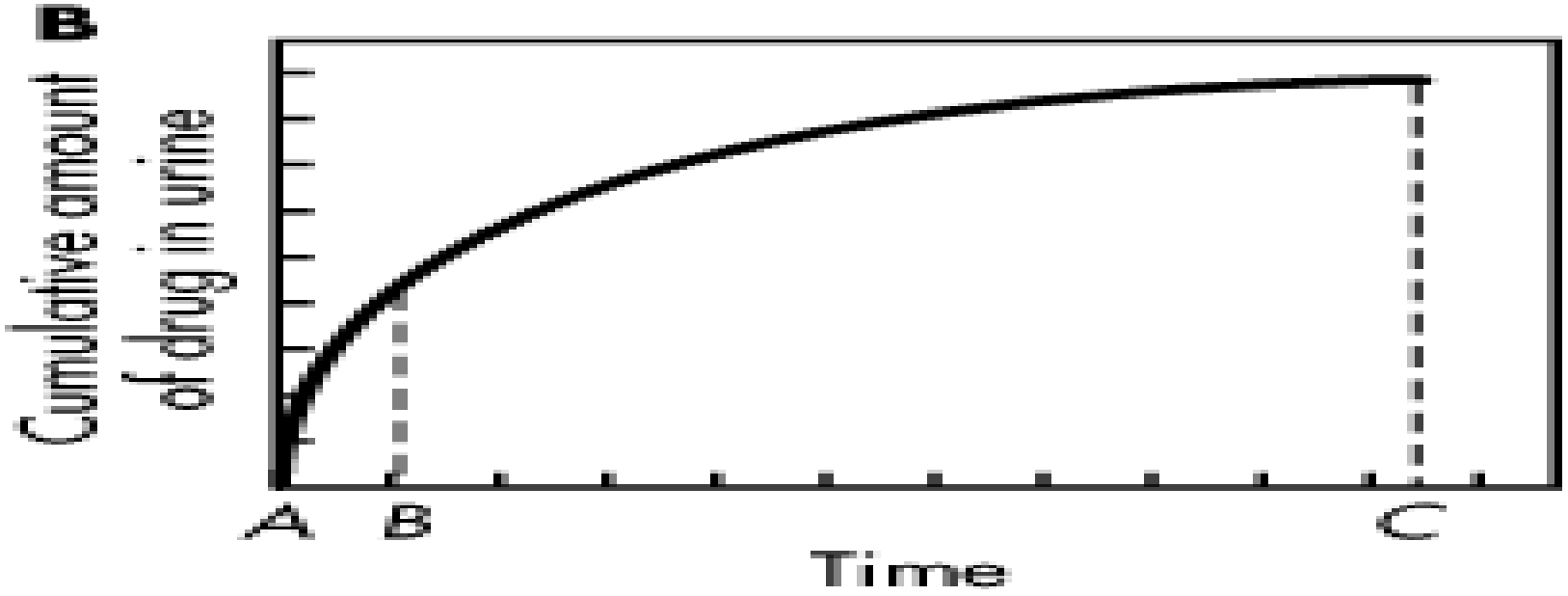
- ***II-Assessment of bioavailability from urine data:***

1- From $Xu^{\infty} = \frac{Ku}{Ke} \cdot Xo$



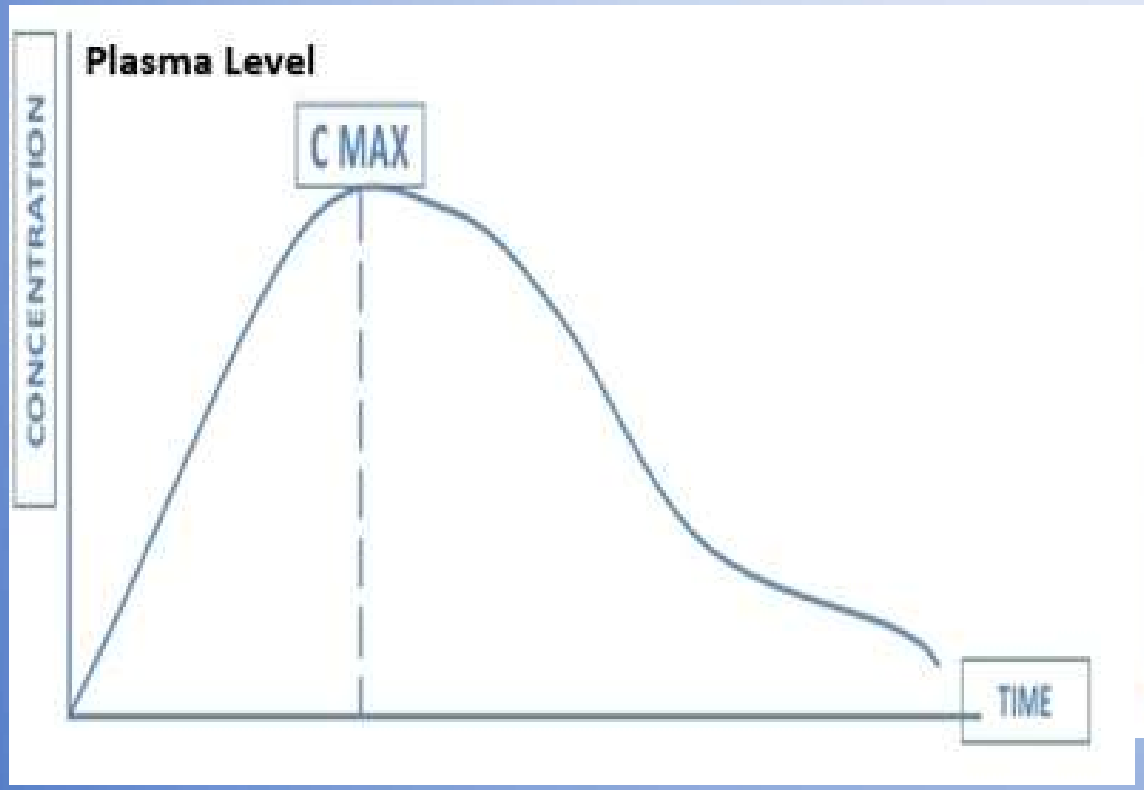


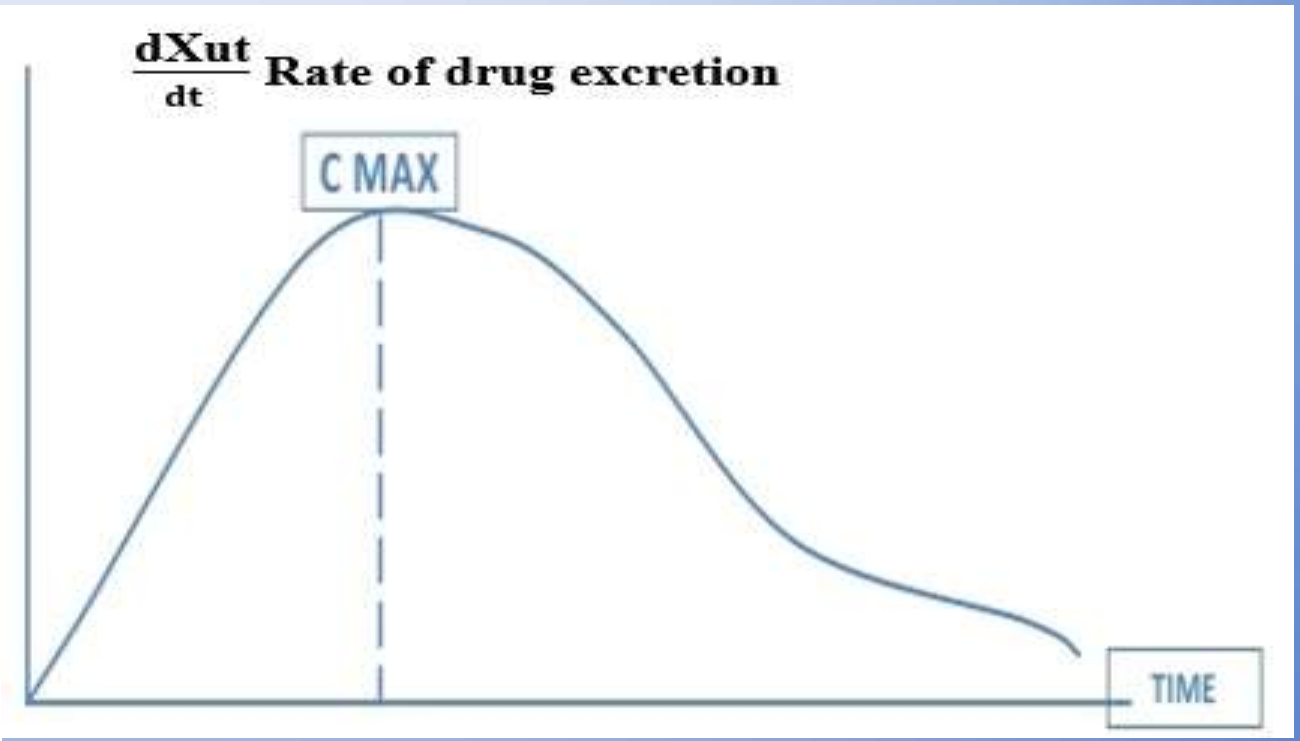

A
Plasma level
A
B
C
Time


B
Cumulative amount of drug in urine
A
B
C
Time

- ***II-Assessment of bioavailability from urine data:***

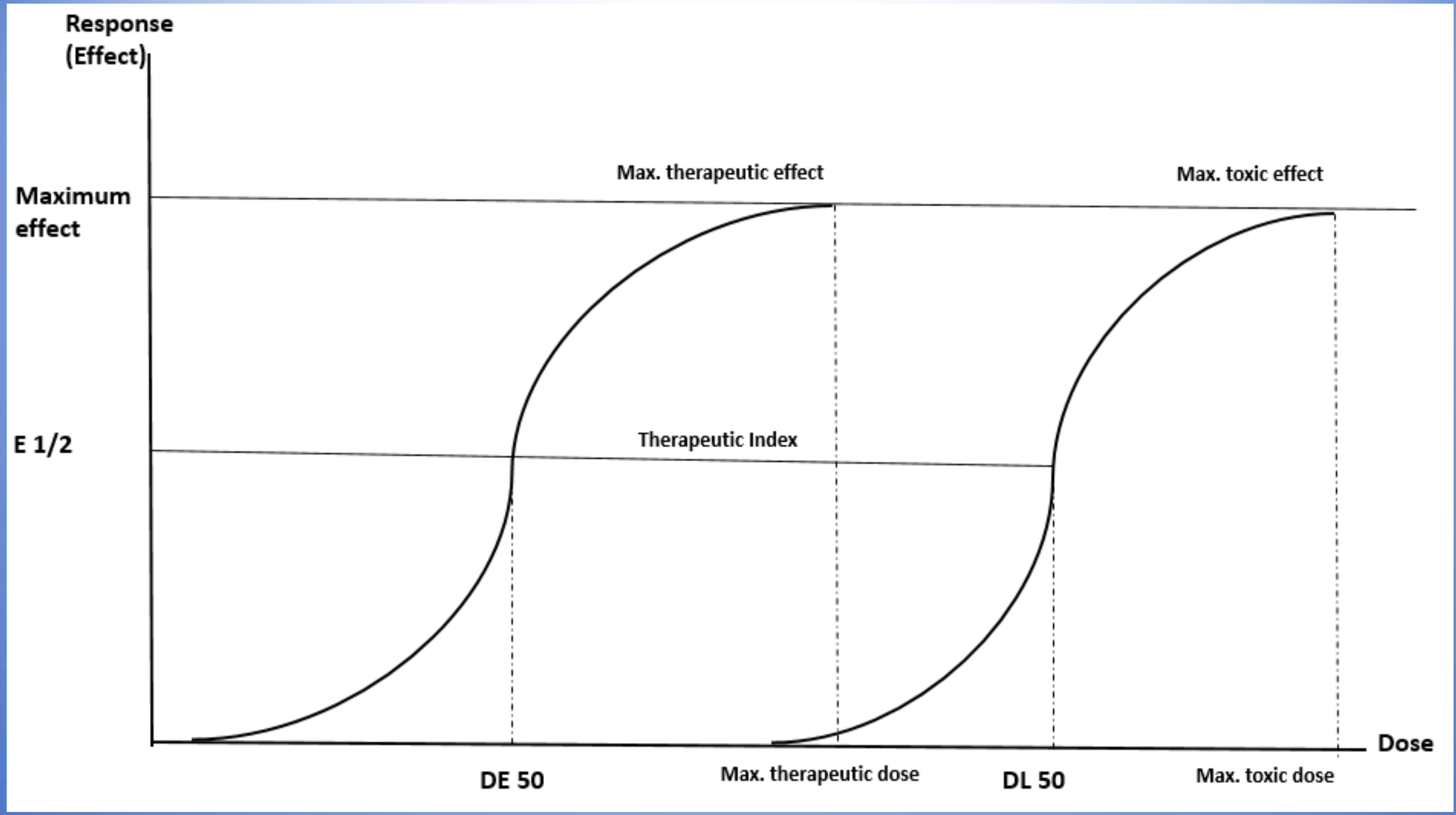
2- From $\frac{dXut}{dt} = Ku \cdot Xo \cdot e^{-ke.t}$

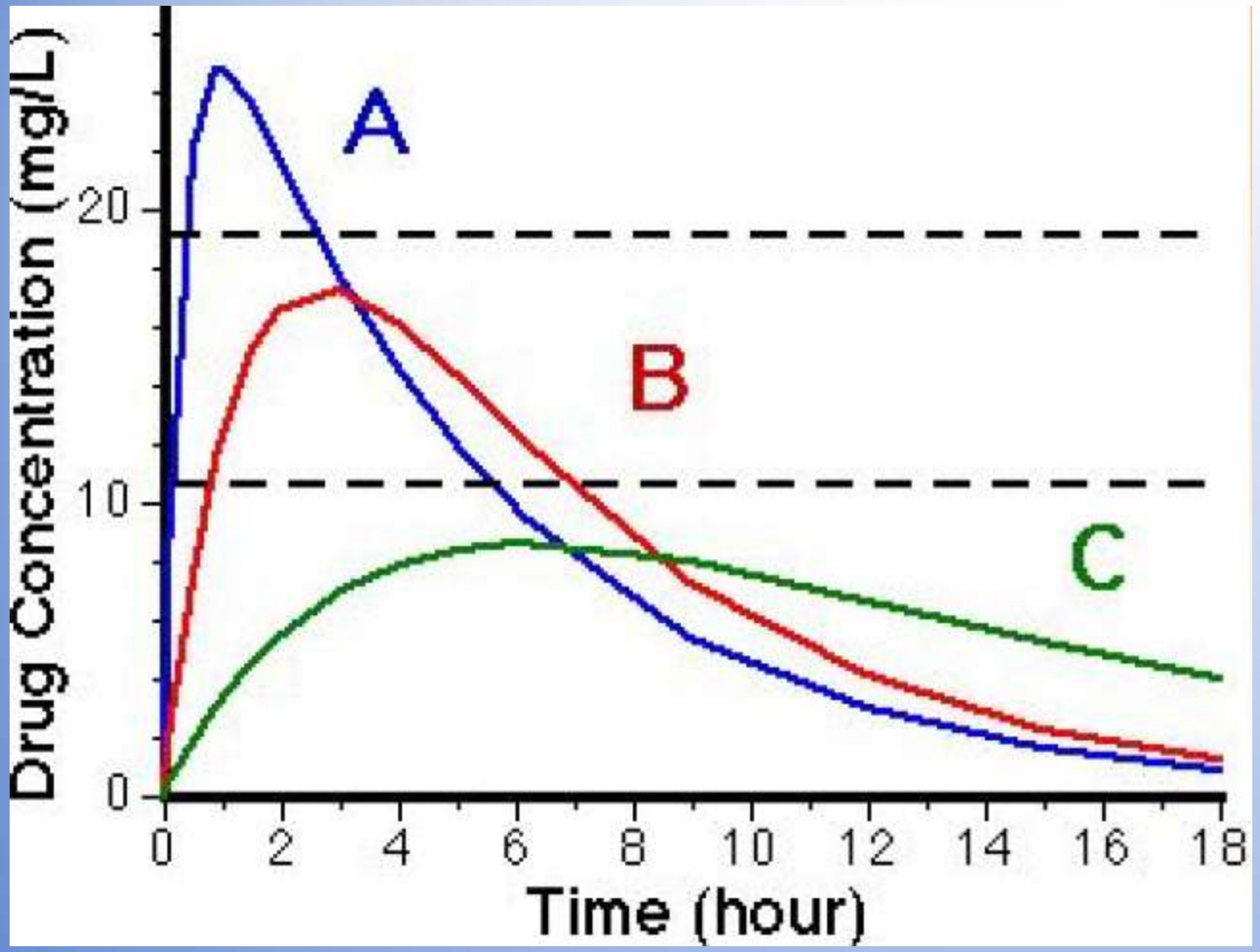




III-Assessment of bioavailability using Acute Pharmacological Effect

- In some cases, the quantitative measurement of a drug in plasma or urine lacks an assay with sufficient accuracy and/or reproducibility. An acute pharmacological effect such as effect on pupil diameter, heart rate, or blood pressure … etc. can be useful as an index of drug bioavailability.
- In this case an acute pharmacological effect- time curve is constructed.
- Measurements of the pharmacological effect should be made with sufficient frequency to permit a reasonable estimate of total area under the curve (AUC) for a time period at least three times the half-life of the drug.
- bioavailability may require demonstration of a dose-related


Response
(Effect)
Maximum
effect
E 1/2
Max. therapeutic effect
Max. toxic effect
Therapeutic Index
Dose
DE 50
Max. therapeutic dose
DL 50
Max. toxic dose



A: highly available , toxic.
B: Reasonable available, Good therapeutic response
C: unavailable, lack of response(therapeutic failure)

- **Determination of bioavailability :**

1- Method of Simpson:

$$(AUC)_0^\infty = \frac{h}{3}(\mathrm{E}+2\mathrm{P}+4\mathrm{I})$$

2- Method of integration of Bateman's equation

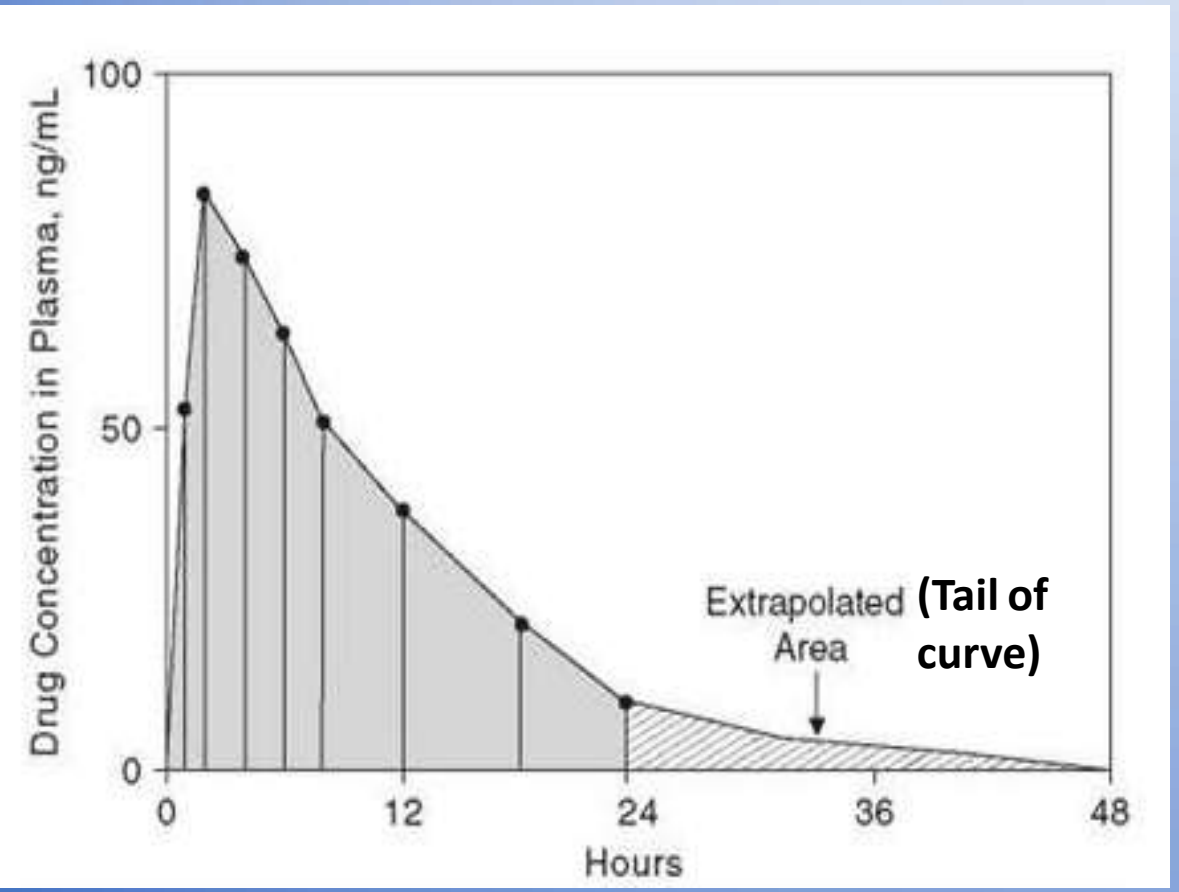
$$(AUC)_0^\infty = \frac{Co}{Ke} = \frac{FXo}{Vd.Ke} = \frac{FXo}{Cl} = \frac{Ao}{Ke}$$

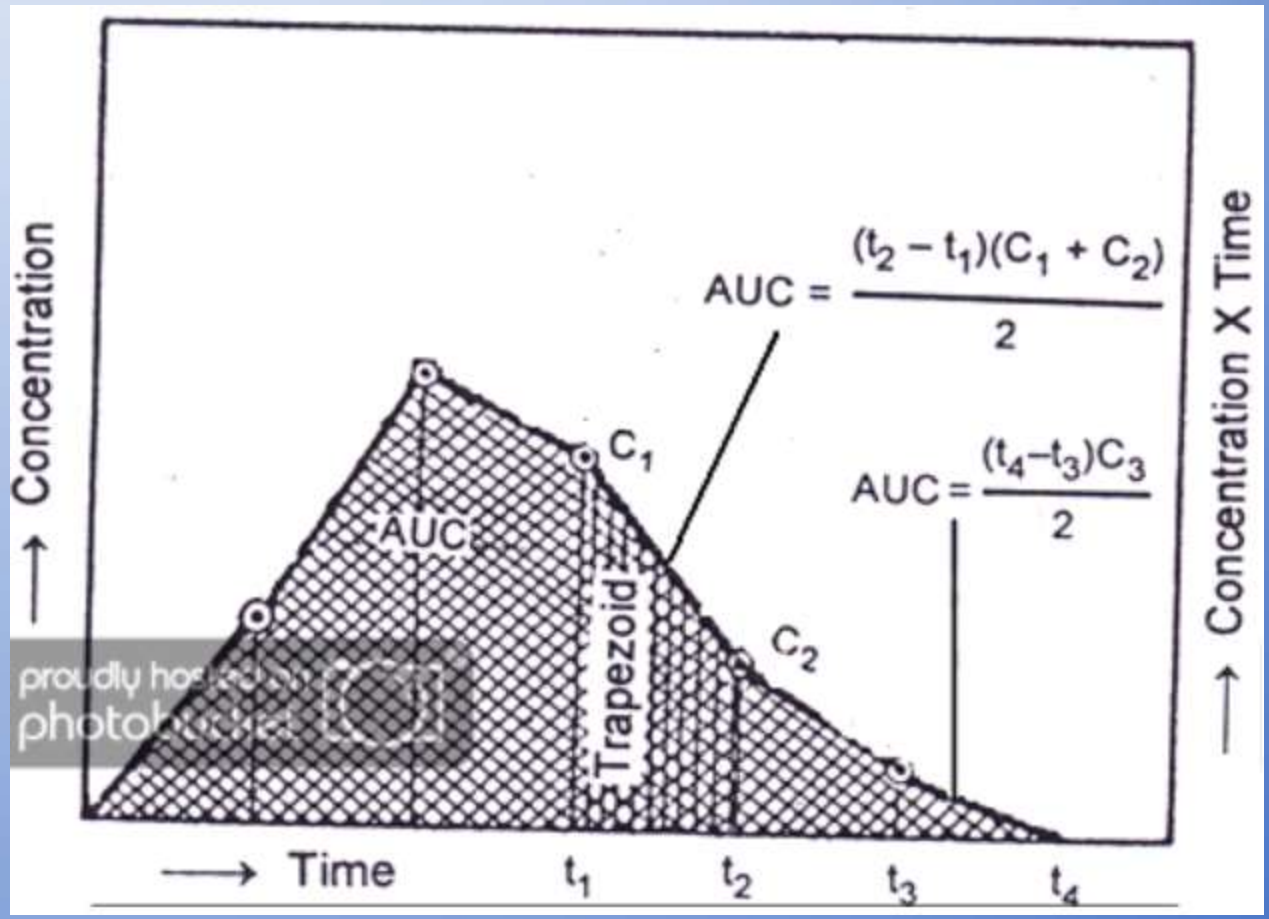
3- The Trapezoidal rule

- It is simplest method and involves breaking up of plasma concentration versus time profile into several trapezoids; calculate area of individual trapezoids and then adding up these areas to arrive at cumulative AUC.
- (AUC) is approximated the $\sum of\ a\ number\ of\ trapezoids$ into which the AUC has been divided.

- **Area** $= (C_O + C_1)(t_1 - t_0)/2 + (C_1+C_2)(t_2-t_1)/2 + \text{----------} + (C_{n-1}+C_n)(t_n-t_{n-1})/2$
- **Area** $= \dfrac{(C_{n-1}+C_n)\,(t_n-t_{n-1})}{2}$
- **The area of tail** $= \dfrac{C\ last}{Ke} = \dfrac{C\ last\ .\ t\ 1/2}{0.693}$
- **AUC** $= \sum \dfrac{(C_{n-1}+Cn)\,(tn-t_{n-1})}{2} + \dfrac{C\ last}{Ke}$

where C last = the last measured concentration





- **Factors affecting Bioavailability**

Factors affecting bioavailability may be classified into :

- ✔ **Drug factors: Drug properties & formulation factors (Technological factors)**
- ✔ **Food influence**
- ✔ **Administration of other drugs**

✔ Drug factors:

1. **Drug properties :** Specific surface area, dissolution rate, MWt, Partition coefficient O/W, Symmetry of moleculs, H bonds, Pka of drug and pH od the medium.
2. **Formulation factors (Technological factors):** influence of excipients as diluent, SAA, viscosity enhancer, lubricant, polymorphism, complexation, disintegrant and tablet compression, coating nature, dosage form.

✔ Food influence decrease drug absorption

Increases the bulk, decrease dissolution of drug, increases viscosity.

Three possibilities of food effect on bioavialabilty

- **Three possibilities of food effect on bioavailability:**

a. **Extent is the same, rate differs.**
b. **The same rate and different extent.**
c. **Increasing extent when taken with food.**

- **This effect of food on the bioavailability of drug is indirectly through effect on :**

1. **Alteration in gastric emptying rate.**
2. **Stimulation of GI secretions.**
3. **Competition between food compound and drugs for specialized absorption mechanism.**

✔ **Administration of other drugs:**

- Drugs interaction absorption level.
- Tetracycline + anti-acid.
- Adsorbent (charcoal)+ Ca.
- Mineral oils + lipo-soluble vitamins decreases laxatives.
- Alcohol + Fe salt increase.
- Metoclopramide + paracetamol increase

- **Pharmaceutically or chemically equivalent products**
- Two or more drug products contain equal amounts of the same therapeutically active ingredient(s) in identical dosage forms, and that these Dosage forms meet the requirements such as (purity, content uniformity and disintegration time) as established by the United States Pharmacopeia and/or National Formulary. But they differ in characteristic such as color, taste, shape, packaging, expiration time and labeling.

- **Pharmaceutical alternatives:**
- Are drug products that contain the same therapeutic moiety but differ in salt or ester form, in the dosage form or in the strength. Also, controlled-release dosage forms are pharmaceutical alternatives when compared with conventional formulations of the same active ingredients.

- **Bioequivalence (Biological Equivalence):**

two or more chemically or pharmaceutically equivalent products produce comparable bioavailability characteristics in any individual when administered in equivalent dosage regimen (parameters compared include the area under the plasma concentration versus time curve (AUC) from time zero to infinity$[AUC]_0^\infty$, maximum plasma concentration(Cpmax) and the time of peak concentration tmax).

- **Therapeutic equivalence**

two or more chemically or pharmaceutically equivalent products essentially produce the same efficacy and/or toxicity in the same individuals when administered in an identical dosage regimen.

- **Therapeutic Alternative**

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. For example, ibuprofen is given instead of aspirin; cimetidine may be given instead of ranitidine.

- **Pharmaceutical substitution**:

The process of dispensing a pharmaceutical alternative for the prescribed drug product. For example, ampicillin suspension is dispensed in place of ampicillin capsules, or tetracycline hydrochloride is dispensed in place of tetracycline phosphate. Pharmaceutical substitution generally requires the physician's approval.

- **Interchangeable Drug Products:**

Pharmaceutics equivalent or bioequivalents that are accepted as therapeutic equivalents.

- **Fundamental concepts :**

The availability of a drug or its active metabolite to the end organ or receptor is controlled by these factors:

1. The rate & extent of release of the drug from the drug product and its subsequent absorption from the solution state.
2. First pass effect.
3. The combined process of plasma protein binding, tissue binding, drug distribution to various body fluids, metabolism and urinary, fecal and/ or lung excretion.