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Introduction

- Bioavailability is defined as rate and extent of absorption of unchanged drug from it's dosage form and become available at the site of action.

- Bioavailability of a drug from it's dosage form depends upon 3 major factors:

  - Pharmaceutical factors
  - Patient related factors
  - Route of administration

Objectives

- 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.

Absolute bioavailability (F)

- When systemic availability of drug administered orally is determined in comparison to its intravenous administration, is called absolute bioavailability.

- Its determination is used to characterize a drug's inherent absorption properties from the extra vascular site.

$$\text{Absolute bioavailability} = \frac{[AUC]oral\ (Dose)iv}{[AUC]iv\ (Dose)oral}$$

Relative Bioavailability (Fr)

- When systemic availability of drug after oral administration is compared with that of an oral standard of same drug (such as an aqueous or non aqueous solution or suspension) it is referred as relative bioavailability.

- It is used to characterize absorption of drug from its formulation.

$$\text{Relative Bioavailability} = \frac{[AUC]test\ (Dose)std}{[AUC]std\ (Dose)test}$$

METHODS OF ASSESSING BIOAVAILABILITY:

PHARMACOKINETIC METHODS

- *Plasma Level- Time Studies*
- *Urinary Excretion Studies*

PHARMACODY NAMIC METHODS

- *Acute Pharmacological Response*
- *Therapeutic Response*

Pharmacokinetic Methods

- Widely used and based on assumption that Pharmacokinetic profile reflects the therapeutic effectiveness of a drug.

Plasma Level- Time Studies:

- Most common type of human bioavailability studies.

- Based on the assumption that there is a direct relationship between the concentration of drug in blood or plasma and the concentration of drug at the site of action.

- Following the administration of a single dose of a medication, blood samples are drawn at specific time intervals and analyzed for drug content.

- A profile is constructed showing the concentration of drug in blood at the specific times the samples were taken.

- Bioavailability (the rate and extent of drug absorption) is generally assessed by the determination of following three parameters.

They are.. C_{max} ***(Peak plasma concentration)***

t_{max}***(time of peak)***

Area under curve

Plasma Drug Concentration- Time Profile

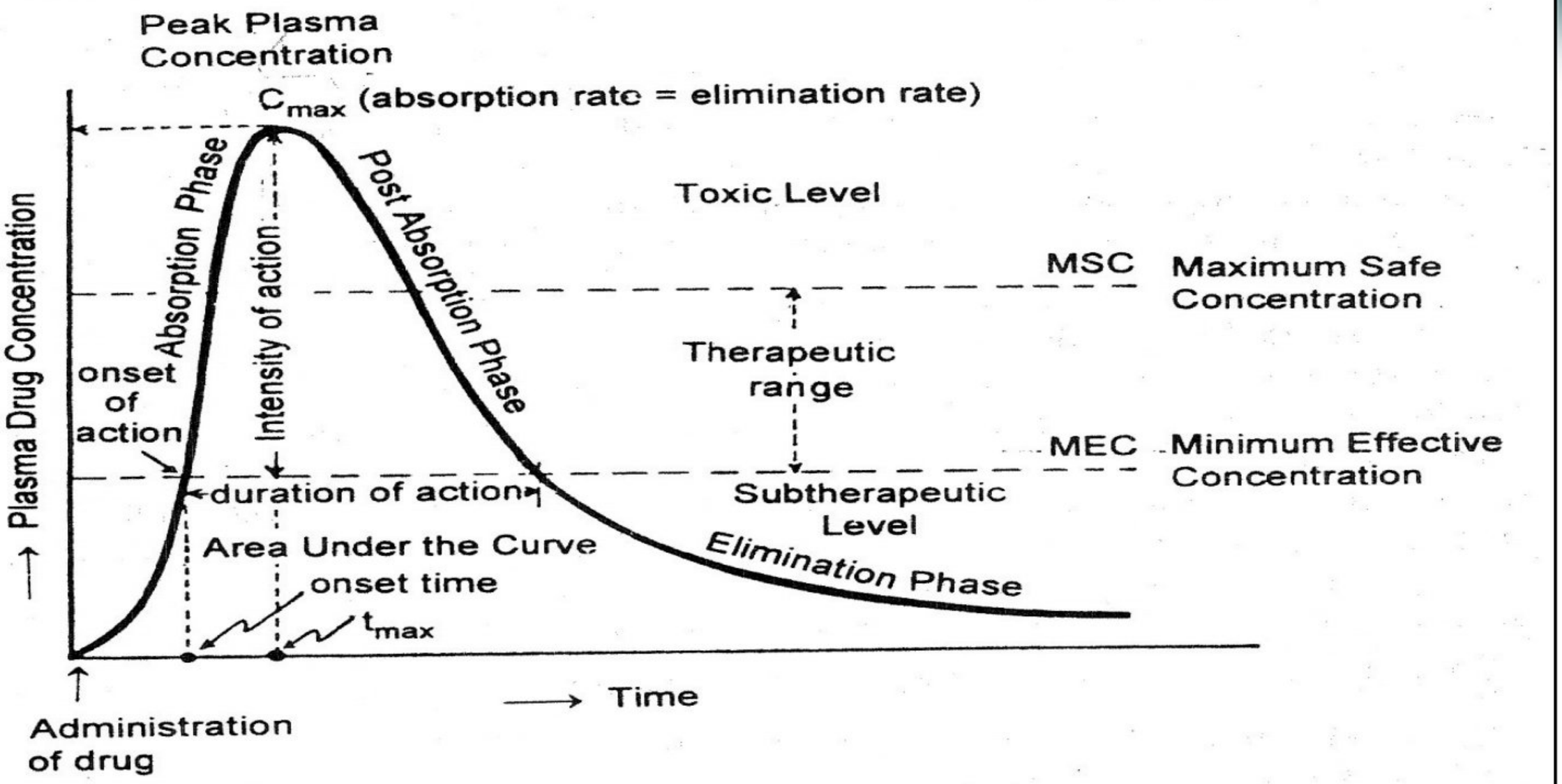


Fig. 9.1 A typical plasma concentration-time profile showing pharmacokinetic and pharmacodynamic parameters, obtained after oral administration of single dose of a drug.

- **C_{max}:** (Peak plasma drug concentration)
  - Maximum concentration of the drug obtained after the administration of single dose of the drug.
  - Expressed in terms of µg/ml or mg/ml.

- **t_{max}:** (Time of peak plasma conc.)

  Time required to achieve peak concentration of the drug after administration.
  - Gives indication of the rate of absorption.
  - Expressed in terms of hours or minutes.

- **AUC:** Is the measurement of the extent of the drug bioavailability

It is the area under the drug plasma level-time curve from t =0 & t = ∞, and is equal to the amount of unchanged drug reaching the general circulation divided by the clearance.

$$[\,AUC]_0^{\infty} = \int_0^{\infty} Cpdt$$

$$[\,AUC]_0^{\infty} = \frac{FD_0}{\text{Clearance}} = FD_0 / kV_D$$

Measurement of AUC

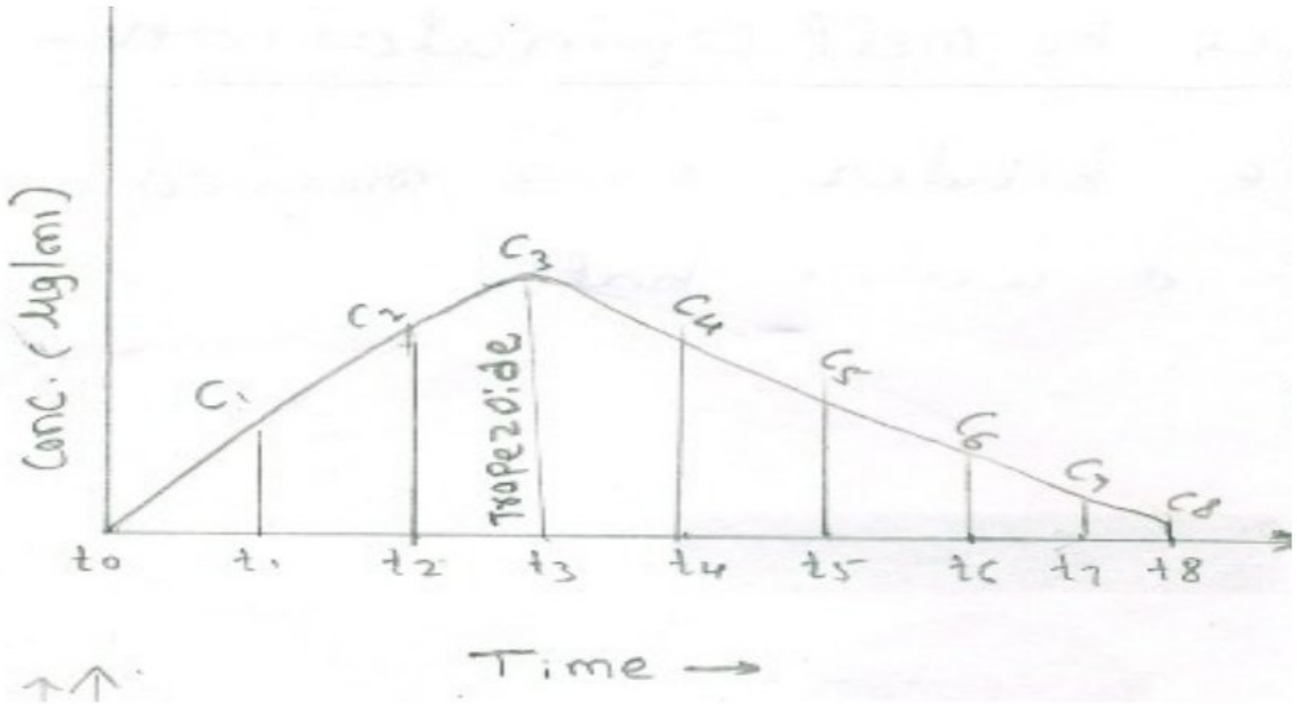
- ***Trapezoidal method:***
  - –Most common method of estimating AUC.
  - –Divide the plasma conc-time curve into several trapezoids.
  - –Count the trapezoids & find the area.
  - –Total area of the trapezoids will approximate the area under the curve.
  - –More number of trapezoids formed more accurate will be the result.

The area of one trapezoid between time t_1 and t_2 is

$$= \frac{C_1 + C_2 (t_2 - t_1)}{2}$$

Thus $$AUC = \frac{C1+C2\,(t2-t1)}{2} + \frac{C2+C3\,(t3-t2)}{2} + \ldots\ldots$$

$$\ldots Cn\text{-}1 + \frac{Cn\,(tn+1-tn)}{2}$$



- ***CUT & WEIGH METHOD:***

  - Preparing calibrated plot by cutting squares of graph &weights are recorded & plotted against weight V_s area.

  - Sample curve is cut & weight is recorded.

  - By interpolation method area of sample graph is found.

- ***PLANIMETER:***
- Instrument for mechanically measuring the area under the curve.
- Measures area by tracing outline of curve.
- Disadvantage:
- Degree of error is high due to instrumental & human error.

- ***COUNTING THE SQUARE :***
- Total no. of squares enclosed in the curve is counted.
- Area of each square determined using relationship:

AREA=(height) (width)

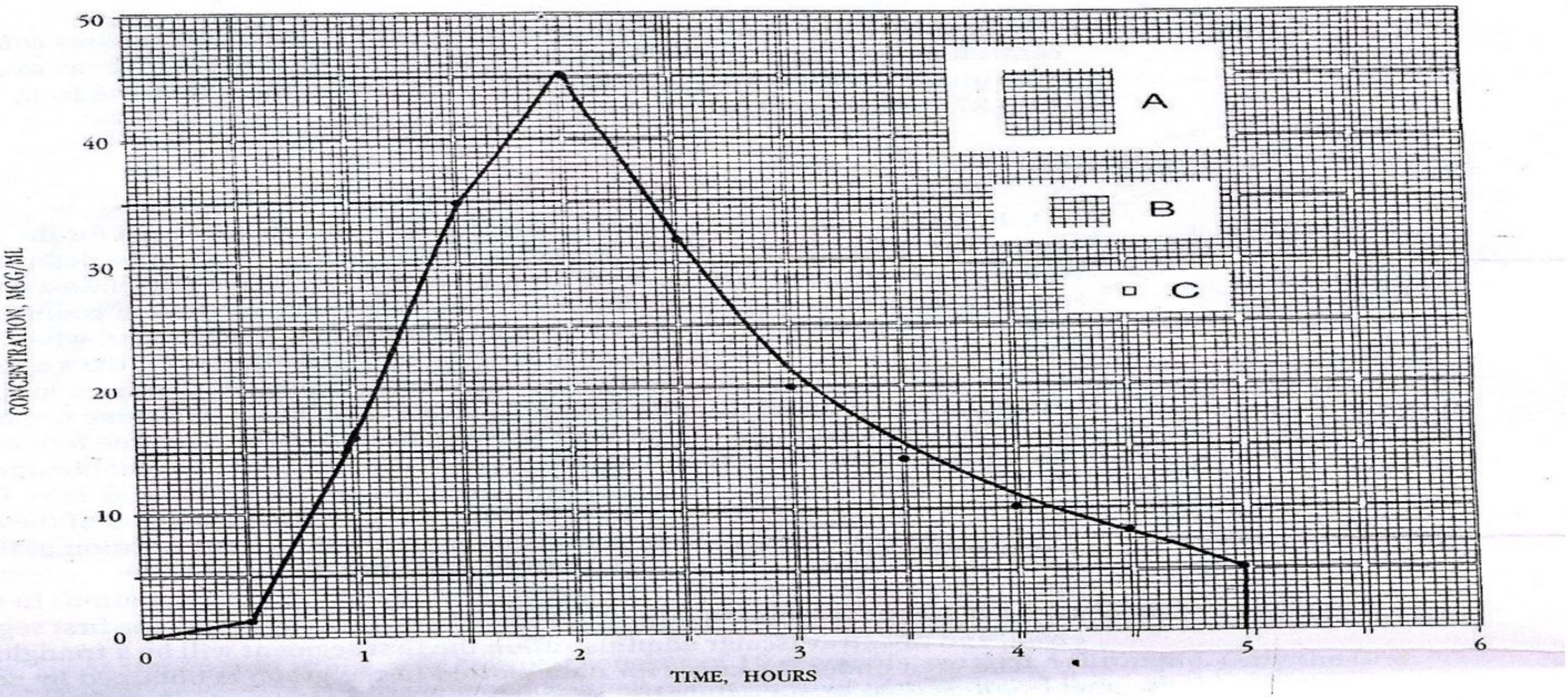


Fig. 6-5: Estimation of Area Under Plasma Concentration versus Time Curve by the Method of Counting Squares.

area of square A = (5.0 mcg/mL) (0.50 hr) = 2.5 mcg•hr/mL,
area of square B = (2.5 mcg/mL) (0.25 hr) = 0.625 mcg•hr/mL, and
area of square C = (0.5 mcg/mL) (0.05 hr) = 0.025 mcg•hr/mL

- The extent of bioavailability can be determined by the following equations:

For single dose study:

$$F = \frac{[AUC]\text{oral Div}}{[\text{AUC}]\text{iv Div}}$$

$$Fr = \frac{[AUC]\text{test Dstd}}{[\text{AUC}]\text{stdDtest}}$$

For multiple dose study:

$$Fr = \frac{[AUC]\text{test Dstd}\tau\text{test}}{[\text{AUC}]\text{stdDtest}\tau\text{std}}$$

$$Fr = \frac{(\text{Css, max})\text{test Dstd }\tau\text{test}}{[\text{Css, max}]\text{stdDtest}\tau\text{std}}$$

Urinary Excretion Studies:

- Urinary excretion of unchanged drug is directly proportional to plasma concentration of drug.

- Thus, even if a drug is excreted to some extent (at least 10 to 20%) in the urine, bioavailability can be determined.

  eg: Thiazide diuretics, Sulphonamides.

- Method is useful when there is lack of sufficiently sensitive analytical technique to measure drug concentration.

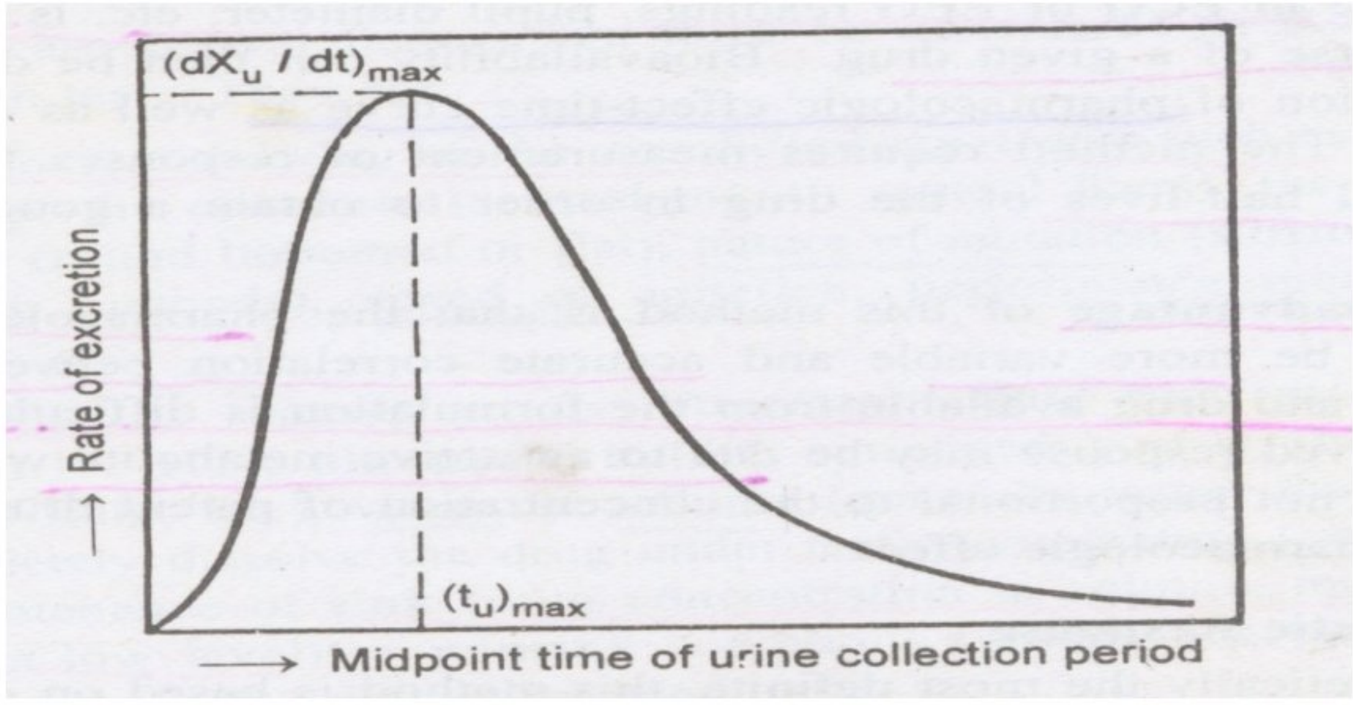
- Noninvasive method, so better patient compliance.

➢ *Three Important Parameters in urine excretion data for single dose study:*

$(dx_u/dt)_{max}$

$(t_u)_{max}$

X_u^{∞}



Plot of urinary excretion rate V_s time

$(dx_u/dt)max$:(Maximum urinary excretion rate)

- Its value increases as rate and/or extent of absorption increases.
- Obtained from peak of plot between rate of excretion versus midpoint time of urine collection period.

(t_u) max:

- Time for maximum excretion rate
- Its value decreases as absorption rate increases.
- Analogues of t_{max} of plasma level data.

X_u^∞:Cumulative amount of drug excreted in urine

- Related to AUC of plasma level data.
- It increases as the extent of absorption increases.

The extent of bioavailability is calculated from equation :

For single dose study:

$$F = \frac{(\mathrm{Xu})\mathrm{oral\ Div}}{(\mathrm{Xu})\mathrm{iv\ \ Doral}}$$

$$Fr = \frac{(\mathrm{Xu})\mathrm{test\ Dstd}}{(\mathrm{Xu})\mathrm{std\ \ Dtest}}$$

For multiple dose study:

$$Fr = \frac{(\mathrm{Xu, ss})\mathrm{test\ Dstd\ \tau test}}{(\mathrm{Xu, ss}]\mathrm{std Dtest \tau std}}$$

Pharmacodynamic methods

Acute Pharmacologic Response Method:

- When bioavailablity measurement by pharmacokinetic method is difficult, an acute pharmacologic effect such as effect on pupil diameter, EEG & ECG readings related to time course of drug.
- Bioavailability can then be determined by construction of pharmacological effect- time curve as well as dose response graphs.

Disadvantage:

- It tends to be more variable.
- Observed response may be due to an active metabolite whose concentration is not proportional to concentration of parent drug.

Therapeutic Response Method:

- This method based on observing the clinical response to a drug formulation given to patient suffering from disease.

Drawbacks:

The major drawbacks of this method is that quantitation of observed response is too improper to allow for reasonable assessment of relative bioavailability between two dosage forms of the same drug.

E.g.: Anti-inflammatory drugs.

❖ Many patients receive more than one drug

Clinical Observations

- Clinical trails in humans establish the safety and effectiveness of the drug products and also used to determine bioavailability.

- The FDA consider this approach only when analytical methods and pharmacodynamic methods are not available.

- Comparative clinical studies have been used to establish bioequivalence for topical antifungal drug product.

  Ex: Ketoconazole

In-Vitro Studies

- Drug dissolution studies may under certain conditions give an indication of drug bioavailability.

- Dissolution studies are often performed in several test formulations of the same drug.

- The test formulation that demonstrates the most rapid rate of drug bioavailability *in-vitro* will generally have the most rapid rate of drug bioavailability *in-vivo*.

- The FDA may also use the other *in-vitro* approaches for establishing bioequivalence.

  Ex: Cholestyramine resin.

CONCEPT OF EQUIVALENCE:

EQUIVALENCE: Relationship in terms of bioavailability, therapeutic response or a set of established standards of one drug product to another.

Objectives:

- If a new product intended to be a substitute for an approved medical product.
- To ensure clinical performance of drugs.
- Equivalence studies are conducted if there is:
  - a) A risk of bio-inequivalence.
  - b) A risk of pharmacotherapeutic failure or diminished clinical safety.

Equivalence may be defined in several ways:

Chemical equivalence:

- ✓ If two or more dosage forms of same drug contain same labelled quantities specified in pharmacopoeia.

  Eg : Dilantin and Eptoin chemically equivalent as they contain same quantity of Phenytoin on chemical assay.

Bioequivalence:

- ✓ The drug substance in two or more identical dosage forms, reaches the systemic circulation at the same relative rate and extent i.e. their plasma concentration-time profiles will be identical without significant statistical differences.

Pharmaceutical equivalents:

Drug products in identical dosage forms that contain same active ingredient(s),i.e , the same salt or ester, are of the same dosage form, use the same route of administration, and are identical in strength or concentration.

Eg : Chlordiazepoxide hydrochloride,5mg capsules.

Pharmaceutical equivalent drug products are:

Same in :

- ✓ Active ingredient and it's quantity
- ✓ Dosage form
- ✓ standards like strength, quality , purity and identity.

- ✓ Disintegration time
- ✓ Dissolution rates

Differ in:

- Shape
- Release mechanisms
- Packing
- Excipients(including colours , flavours , preservatives)
- labeling

Pharmaceutical alternatives:

- ✓ Drug product that contain the same therapeutic moiety but as different salts, esters or complexes.

Eg: Tetracyclin phosphate or Tetracyclin hydrochloride equivalent to 250mg Tetracyclin base are consider as pharmaceutical alternatives.

pharmaceutical substitution:

- ✓ The process of dispensing a pharmaceutical alternative for the prescribed drug product.

Eg: Ampicillin suspension is dispensed in place of Ampicillin capsules.

Tetracyclin hydrochloride is dispensed in place of Tetracyclin phosphate.

NOTE: Pharmaceutical substitution generally requires the physician's approval.

Therapeutic equivalents:

- ✓ Drug products consider to be therapeutic equivalence only if they are pharmaceutical equivalence and if they can be expected to have a same clinical effect and safety profile when administered to patient specified in the labeling.

- ✓ FDA classifies as therapeutically equivalent those products that meet the fallowing general criteria:

1)They approved as safe and effective.

2)They are pharmaceutically equivalents.

3)They are bioequivalence.

4)They are adequately labeled .

5)They are manufactured in compliance with current GMP regulations.

Therapeutic alternatives:

- ✓ Drug products containing different active ingredients that are indicated for the same therapeutic or clinical objectives.

  Eg: Ibuprofen is given instead of Aspirin.

  Cimetidine instead of Ranitidine.

Therapeutic substitution:

- ✓ The process of dispensing a therapeutic alternative in place of the prescribed drug product.

  Eg: Ampicillin is dispensed instead of Amoxicillin.

  Ibuprofen is dispensed instead of Naproxen.

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