ASSESSMENT OF BIOAVAILABILITY

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Bioavailability

Bioavailability is the measurement of relative amount of drug and the rate at which the drug reaches the systemic circulation from its dosage form and becomes available at the site of action.

Bioavailability fraction (F), refers to the fraction of administered dose that enters the systemic circulation.

$$F = \frac{\text{Bioavailable dose}}{\text{Administered dose}}$$

Bioavailability of a drug from its dosage form depends upon 3 major factors:

1. Pharmaceutical factors
2. Patient related factors
3. Route of administration

OBJECTIVES

- Development of new formulations
- Determination of influence of excipients, patient related factors & 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

Compares the bioavailability of the active drug in systemic circulation following non-intravenous administration with the same drug following intravenous administration

For drugs administered intravenously, bioavailability is 100%

Determination of the best administration route

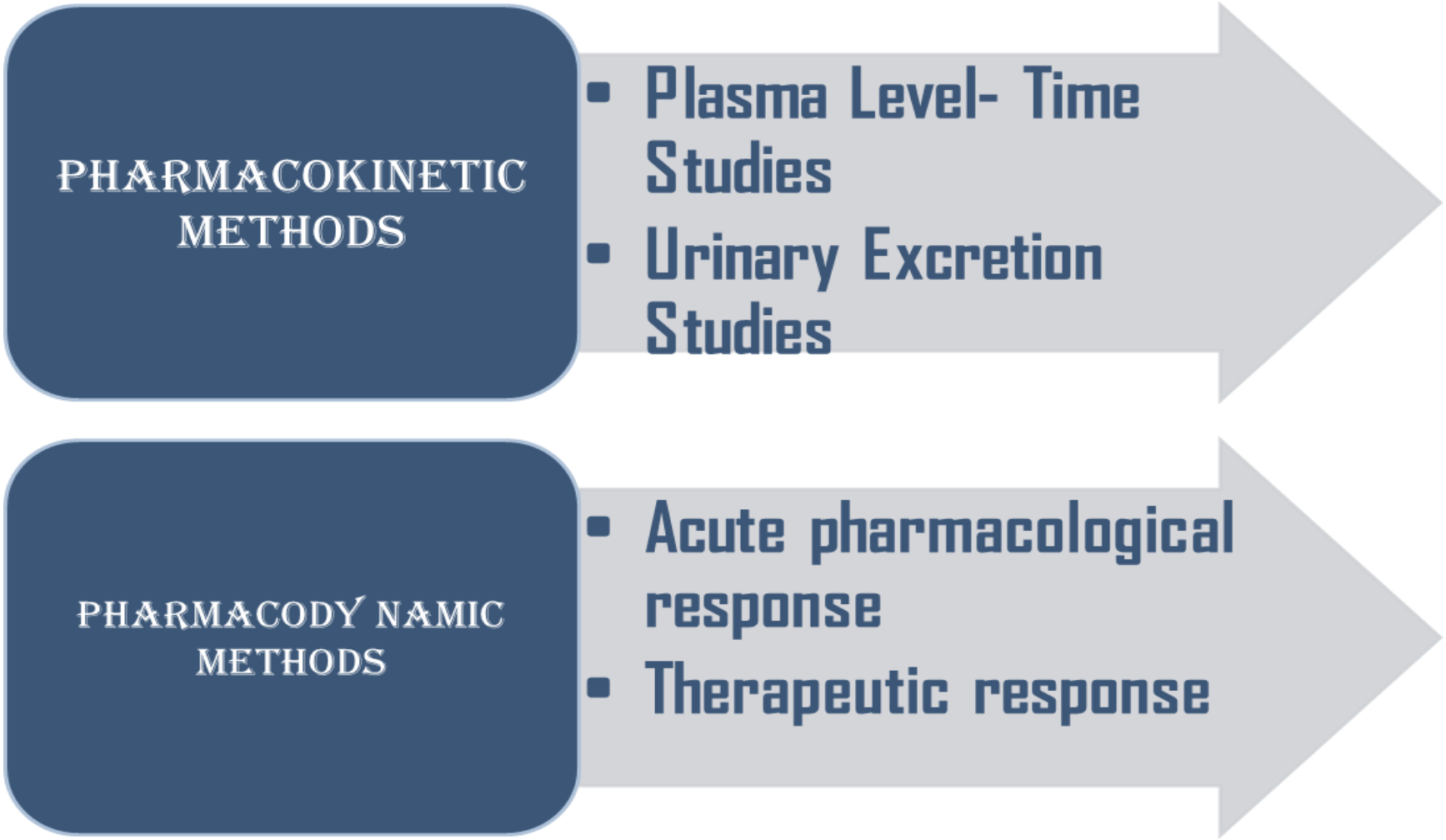
$$F_{ab} = \frac{(AUC)_{drug}}{(AUC)_{IV}}$$

➢ Relative Bioavailability

When systemic availability of drug after oral administration is compared with that of an oral standard of same drug, it is referred to as relative bioavailability

$$F_{rel} = \frac{[AUC]Test\ (Dose)Std}{[AUC]Std\ (Dose)Test}$$

METHODS OF ASSESSMENT OF BIOAVAILABILITY



PHARMACOKINETIC METHOD
PLASMA LEVEL TIME STUDY

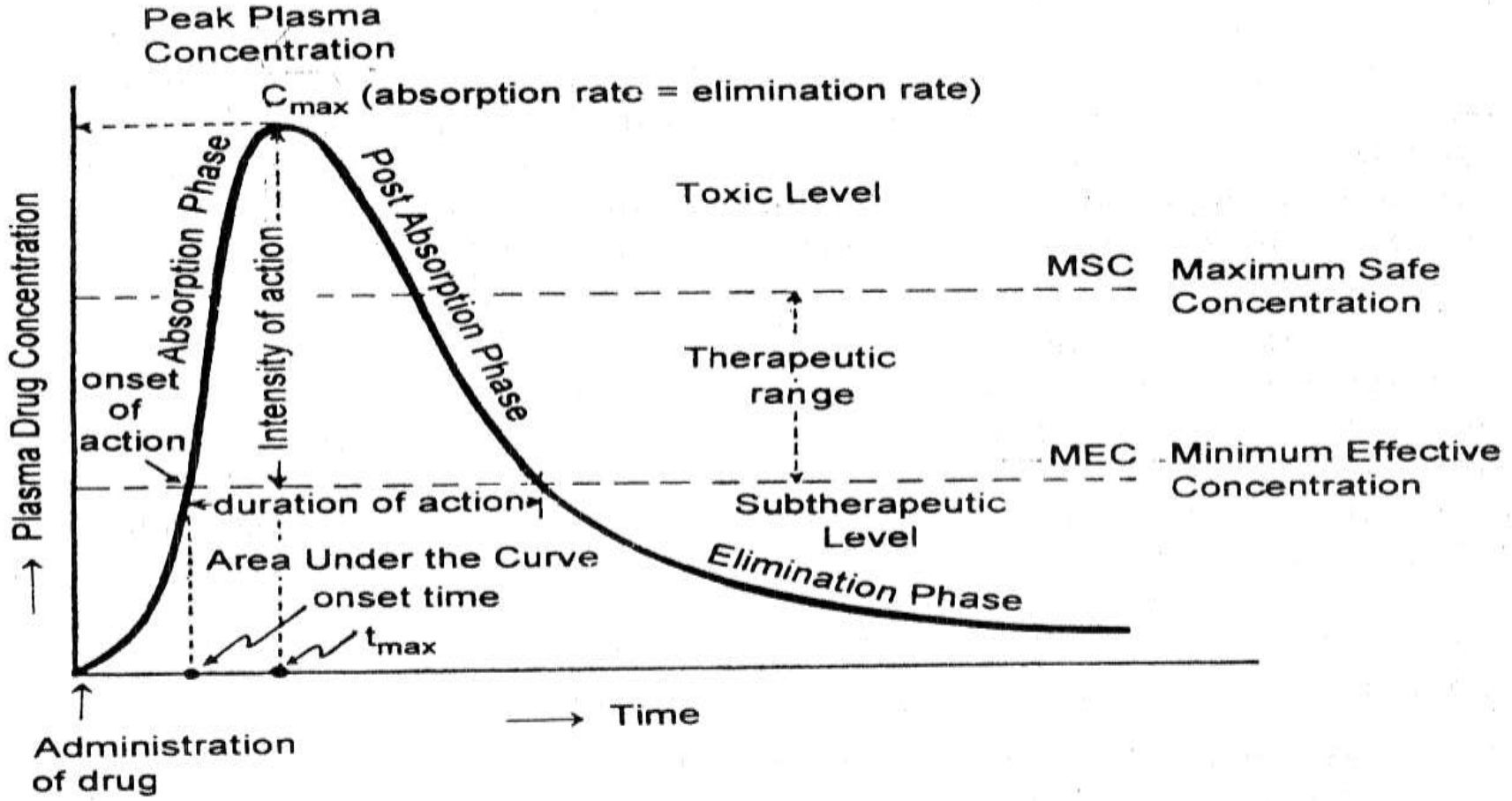


Fig. 9.1 A typical plasma concentration-time profile showing pharmacokinetic and pharmacodynamic parameters, obtained after oral administration of single dose of a drug.

Bioavailability Parameters

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

1. **C_{max} (*peak plasma 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

2. **T_{max} (*time of peak)***

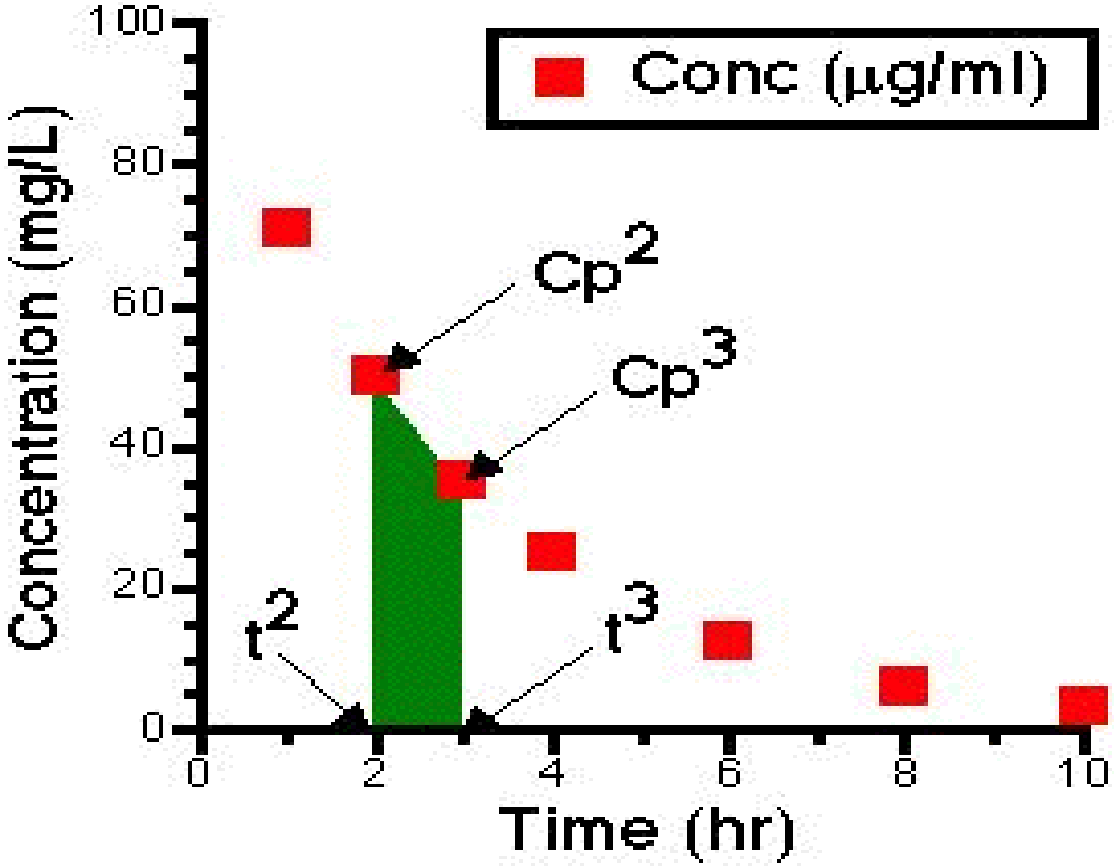
   Time required to achieve peak concentration of the drug after administration. Gives indication of the rate of absorption

   Expressed in terms of hours or minutes

3. **Area under the curve (AUC)**

- It is the measurement of the extent of the drug bioavailability

CALCULATION OF AUC: Trapezoidal Rule



$$AUC_{2\text{-}3} = \frac{Cp^2 + Cp^3}{2} x\,(t_3 - t_2)$$

Single Oral Dose Method

Collection of serial blood samples for a period of 2 to 3 biological half-lives after drug administration

Plot of concentration vs time to obtain the plasma level time profile

At least 3 points should be taken on the ascending part of the curve for accurate determination of ka

Single IV Dose Method

Sampling should start within 5 minutes of drug administration and subsequent samples taken at 15 minute intervals

Plot of concentration vs time to obtain the plasma level time profile

To describe disposition phase, atleast 3 sample points should be taken if the drug follows one-compartment kinetics & 5 to 6 points if it fits two-compartment model

MULTIPLE DOSE STUDY

Drug administration for at least 5 biological half-lives with a dosing interval equal to or greater than the biological half-life to reach the steady-state

A blood sample should be taken at the end of previous dosing interval & 8 to 10 samples after the administration of next dose

URINARY EXCRETION STUDY

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.
Noninvasive method, so better patient compliance.
Eg: Thiazide diuretics, Sulphonamides

Collection of urine at regular intervals for a time span equal to 7 biological half-lives

Analysis of unchanged drug in the collected sample

Determination of the amount of drug excreted in each interval and cumulative amount excreted

BIOAVAILABILITY PARAMETERS

Three important parameters in urine excretion data for single dose study:

1. $(dx_u/dt)_{max}$ (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

2. $(t_u)_{max}$

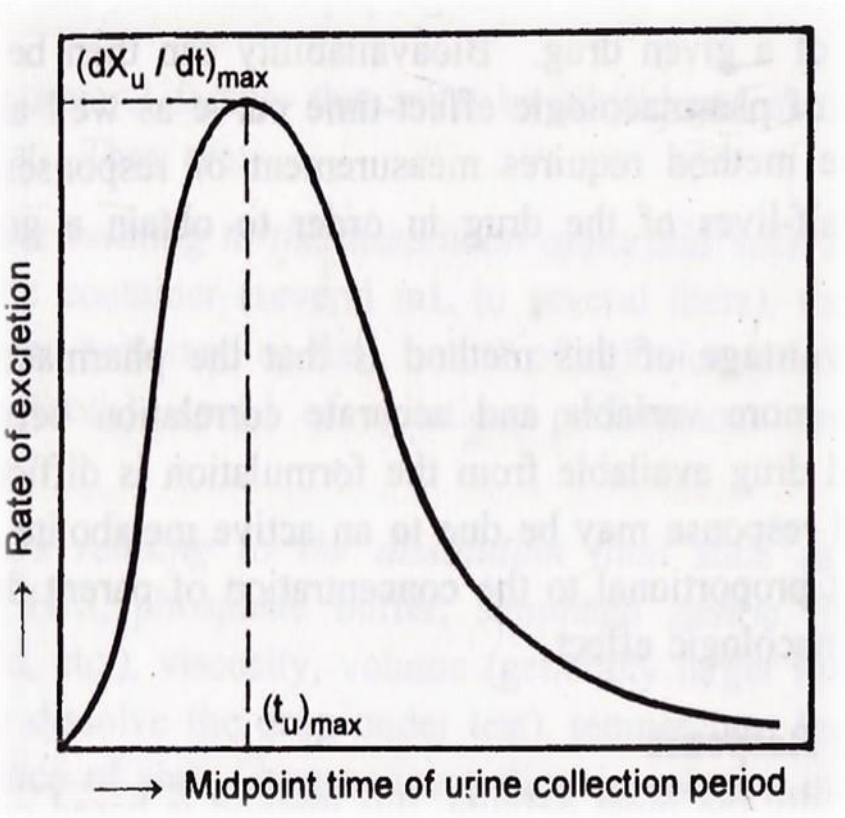
(Time for maximum excretion rate)

Its value decreases as absorption rate increases

Analogues of t_{max} of plasma level data

3. Xu^{∞}

Cumulative amount of drug excreted in urine. It increases as the extent of absorption increases



PHARMACODYNAMIC METHODS

1. ACUTE PHARMACOLOGICAL RESPONSE METHOD

- When bioavailability measurement by pharmacokinetic method is difficult, inaccurate or non-reproducible, an acute pharmacologic method is used
- Bioavailability can then be determined by construction of pharmacological effect- time curve as well as dose response graphs
- Method requires measurement of responses for at least 3 biol2o1gical half-life of the drug in order to obtain a good estimate of AUC

2. THERAPEUTIC RESPONSE METHOD

- This method based on observing the clinical response to a drug formulation given to patient suffering from disease
- A major drawback of this method is that quantization of observed response is too improper to allow for reasonable assessment of relative bioavailability between two dosage forms of the same drug

CONCLUSION

- Bioavailability is a key pharmacokinetic parameter which must be systematically estimated for a new drug formulation or a new modality of administration
- Bioavailability studies are drug product performance studies used to define the effect of changes in the physicochemical properties of the drug substance, the formulation of the drug, manufacturing process of the drug product