BIOAVAILABILITY AND BIOEQUIVALENCE

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BIOAVAILABILITY AND BIOEQUIVALENCE:

Bioavailability: is defined as the rate and extent (amount) of absorption of unchanged drug from its dosage form.

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

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

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

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.

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

Objectives of Bioavailability Studies:

Bioavailability studies are important in the:

1. Primary **stages of development** of a suitable dosage form for a new drug entity to obtain evidence of its therapeutic utility.
2. **Determination of influence of excipients, patient related factors** and possible interaction with other drugs on the efficiency of absorption
3. Development of new formulations of **the existing drugs**.
4. Control of quality of a drug product during the early stages of marketing in order to determine the **influence of processing factors, storage and stability on drug absorption.**
5. Comparison of **availability of a drug substance from different dosage forms or from the same dosage form produced by different manufacturers.**

Measurement of Bioavailability:

The methods employed in the quantitative evaluation of bioavailability are broadly divided into:

1) Pharmacokinetic Methods:

These are indirect methods as they are based on the assumption that the pharmacokinetic properties of a drug reveal its therapeutic efficacy.

The two major pharmacokinetic methods are:

i) Plasma level-time studies, and

ii) Urinary excretion studies.

2)Pharmacodynamic Methods:

These methods are complementary to pharmacokinetic approaches and involve direct measurement of drug effect on a pathophysiologic process as a function of time.

The two Pharmacodynamic methods for determination of bioavailability from:

i) Acute pharmacologic response, and

ii) Therapeutic response.

Plasma Level—Time Studies:

- The method is based on the assumption that two dosage forms that exhibit superimposable plasma level time profiles in a group of subjects should result in identical therapeutic activity.
- With single dose study, the method requires collection of serial blood samples for a period of 2 to 3 biological half-lives after drug administration, their analysis for drug concentration and making a plot of concentration versus corresponding time of sample collection to obtain the plasma level-time profile.
- With i.v. dose, sampling should start within 5 minutes of drug administration and subsequent samples taken at 15 minute intervals.
- To adequately describe the disposition phase, at least 3 sample points should be taken if the drug follows one-compartment kinetics and 5 to 6 points if it fits two compartment model.
- For oral dose, at least 3 points should be taken on the ascending part of the curve for accurate determination of Ka.
- The points for disposition or descending phase of the curve must be taken in a manner similar to that for i.v. dose.

The 3 parameters of plasma level-time studies which are considered important for determining bioavailability are:

1. Cmax:

The peak plasma concentration that gives an indication whether the drug is sufficiently absorbed systemically to provide a therapeutic response. It is a function of both the rate and extent of absorption. Cmax will increase with an increase in the dose, as well as with an increase in the absorption rate.

2. tmax:

The peak time that gives an indication of the rate of absorption. It decreases as the rate of absorption increases.

3. AUC:

The area under the plasma level-time curve that gives a measure of the extent of absorption or the amount of drug that reaches the systemic circulation

The extent of bioavailability can be determined by following equations:

$$F = \frac{[AUC]_{oral}\, D_{iv}}{[AUC]_{iv}\, D_{oral}}$$

$$F_r = \frac{[AUC]_{test}\, D_{std}}{[AUC]_{std}\, D_{test}}$$

With multiple dose study, the method involves drug administration for at least 5 biological half-lives with a dosing interval equal to or greater than the biological half-life (i.e. administration of at least 5 doses) to reach the steady-state. A blood sample should be taken at the end of previous dosing interval and 8 to 10 samples after the administration of next dose.

The extent of bioavailability is given as:

$$F_r = \frac{[AUC]_{test}\, D_{std}\, \tau_{test}}{[AUC]_{std}\, D_{testl}\, \tau_{std}}$$

Where, [AUC] values = Area under the plasma level-time curve of one dosing interval in a multiple dosage regimen, after reaching the steady-state, τ = Dosing interval

Bioavailability can also be determined from the peak plasma concentration at steady-state (Css,max) as follows:

$$F_r = \frac{(C_{ss,max})_{test} D_{std} \tau_{test}}{(C_{ss,max})_{std} D_{testl} \tau_{std}}$$

The absorption rate is not important in multiple dosing methods.

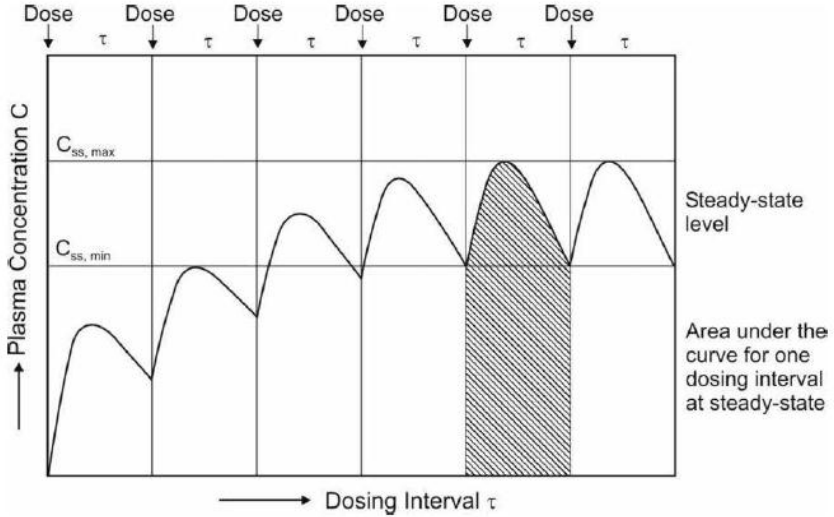


Fig. 11.1 Determination of AUC and $C_{ss,max}$ on multiple dosing upto steady-state

Urinary Excretion Studies:

This method of assessing bioavailability is based on the principle that the urinary excretion of unchanged drug is directly proportional to the plasma concentration of drug.

As a rule of thumb, determination of bioavailability using urinary excretion data should be conducted only if at least 20% of administered dose is excreted unchanged in the urine.

The study is particularly useful for –

- Drugs extensively excreted unchanged in the urine – for example, certain thiazide diuretics and sulphonamides.
- Drugs that have urine as the site of action - for example, urinary antiseptics such as nitrofurantoin and hexamine.

Concentration of metabolites excreted in urine is never taken into account in calculations since a drug may undergo presystemic metabolism at different stages before being absorbed.

Urinary Excretion Studies:

This method involves:

- ❑ **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.**

For obtaining valid results, following criteria must be met further –

- ❑ **At each sample collection, total emptying of the bladder is necessary to avoid errors resulting from addition of residual amount to the next urine sample.**
- ❑ **Frequent sampling of urine is also essential in the beginning in order to compute correctly the rate of absorption.**
- ❑ **The fraction excreted unchanged in urine must remain constant.**

The three major parameters examined in urinary excretion data obtained with a single dose study are:

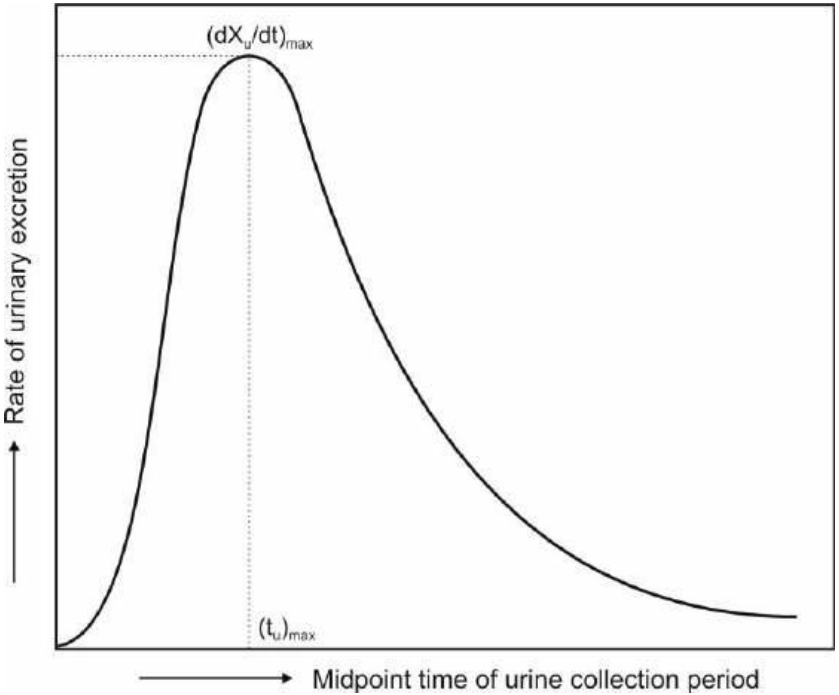
1. **(dXu/dt)max:**

The maximum urinary excretion rate, it is obtained from the peak of plot between rate of excretion versus midpoint time of urine collection period. It is analogous to the Cmax derived from plasma level studies since the rate of appearance of drug in the urine is proportional to its concentration in systemic circulation. Its value increases as the rate of and/or extent of absorption increases.

2. **(tu)max:**

The time for maximum excretion rate, it is analogous to the tmax of plasma level data. Its value decreases as the absorption rate increases.

3. **Xu** : The cumulative amount of drug excreted in the urine, it is related to the AUC of plasma level data and increases as the extent of absorption increases.



Plot of urinary excretion rate versus time. Note that the curve is analogous to a typical plasma level-time profile obtained after oral administration of a single dose of drug.

The extent of bioavailability is calculated from equations given below:

$$F = \frac{\left(X_u^{\infty}\right)_{oral} D_{iv}}{\left(X_u^{\infty}\right)_{iv} D_{oral}}$$

$$F_r = \frac{\left(X_u^{\infty}\right)_{test} D_{std}}{\left(X_u^{\infty}\right)_{std} D_{testl}}$$

With multiple dose study to steady-state, the equation for computing bioavailability is:

$$F_r = \frac{\left(X_{u,ss}\right)_{test} D_{std}\ \tau_{test}}{\left(X_{u,ss}\right)_{std} D_{testl}\ \tau_{test}}$$

Where, (Xu,ss) = Amount of drug excreted unchanged during a single dosing interval at steady-state

2)Pharmacodynamic Methods:

Acute Pharmacologic Response:

- When pharmacokinetic methods cannot be used successfully and easily to measure bioavailability, an inaccurate, non -reproducible, or an acute pharmacologic effect such as change in ECG or E EG readings, pupil diameter, etc., is related to the time course of a given drug.
- Then bioavailability can be determined by making of pharmacologic effect -time curve and dose –response graphs. For this method, responses of the drug for not less than 3 biological half-lives should be measured to obtain a good estimate of AUC.
- The method of acute pharmacologic response has a disadvantage that the pharmacologic response may vary and thus an accurate correlation between the measured response and drug available from the formulation cannot be established.
- Also, the observed response may be due to an active metabolite whose concentration is not proportional to the concentration of parent drug inducing the pharmacologic effect.

Therapeutic Response:

The therapeutic response method involves observing the clinical response of a drug formulation in patients who are suffering from the disease for which the drug is intended to be used. The therapeutic response method has several disadvantages:

1) Quantitation of observed response is so inappropriate that reasonable assessment of relative bioavailability between two dosage forms of the same drug cannot be done.

2) Bioequivalence studies are conducted using a crossover design in which each subject is given each test dosage form, and it is anticipated that the subject's physiological status does not change during the entire study.

3) If multiple - dose protocols for a drug are not employed, a patient who requires the drug for a disease will be administered only a single dose of the drug in every few days or each week.

4) Many patients receive more than one drug, and the bioavailability study results obtained could be compromised because of a drug-drug interaction.