BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES

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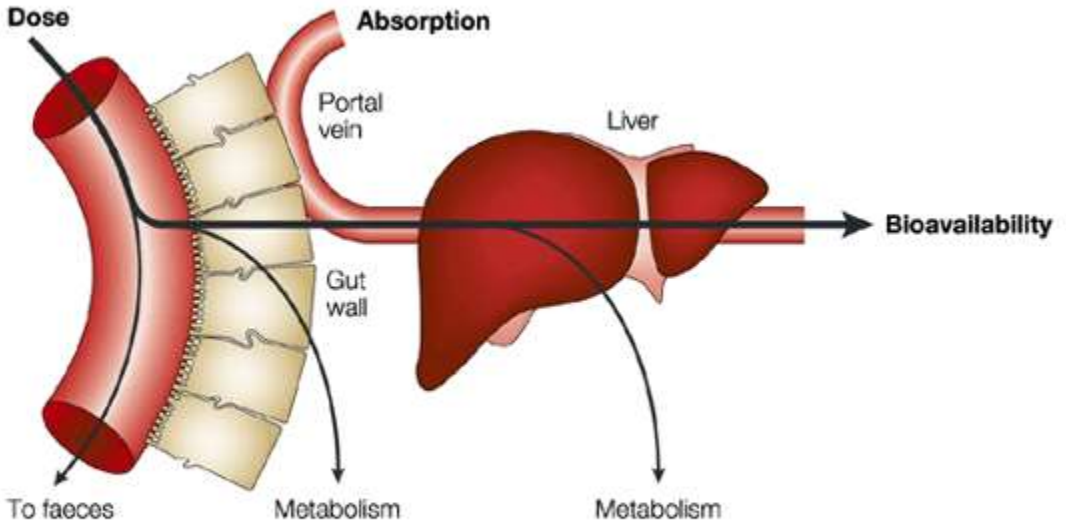
BIOAVAILABILITY :

Bioavailability is the rate and extent of drug that reaches systemic circulation in an unchanged form so as to provide desired therapeutic activity.



OBJECTIVES

- Development of a **new dosage form** for a **new drug entity.**

- 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 and stability on drug absorption.**

- *Development of **new formulations** for the existing drug.*

  Ex: Aspirin

Normal Tablets

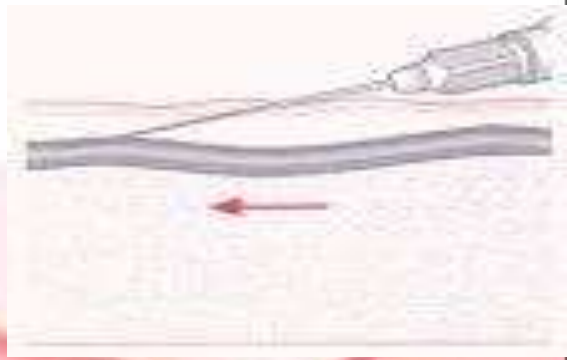
Soluble tablets

Buffered Aspirin Tablets

BIOAVAILABILITY –ABSOLUTE (VS) RELATIVE

Absolute bioavailability **(F) :-** *it is the measure of* ***systemic availability*** *of drug moiety in comparison with the* ***intravenously*** *administered dosage form of the* ***same drug.***

$$F = \frac{[AUC]_{oral} \cdot DOSE_{iv}}{[AUC]_{iv} \cdot DOSE_{oral}}$$



Significance: *To characterize a drugs* ***inherent absorption property*** *from the extra vascular site.*

***Relative bioavailability* (Fr) :-** *it is the measure of systemic availability of a particular drug from a test dosage form is in comparison with the standard dosage form of similar type.*

$$Fr = \frac{[AUC]test.\ DOSE\ std}{[AUC]std.\ DOSE\ test}$$

Significance:

To characterize absorption of a drug from its formulation.

F and Fr are generally expressed in percentages.

Standard

Test

HUMANVOLUNTEERS- healthy subjects (vs.) patients (as per FDA)

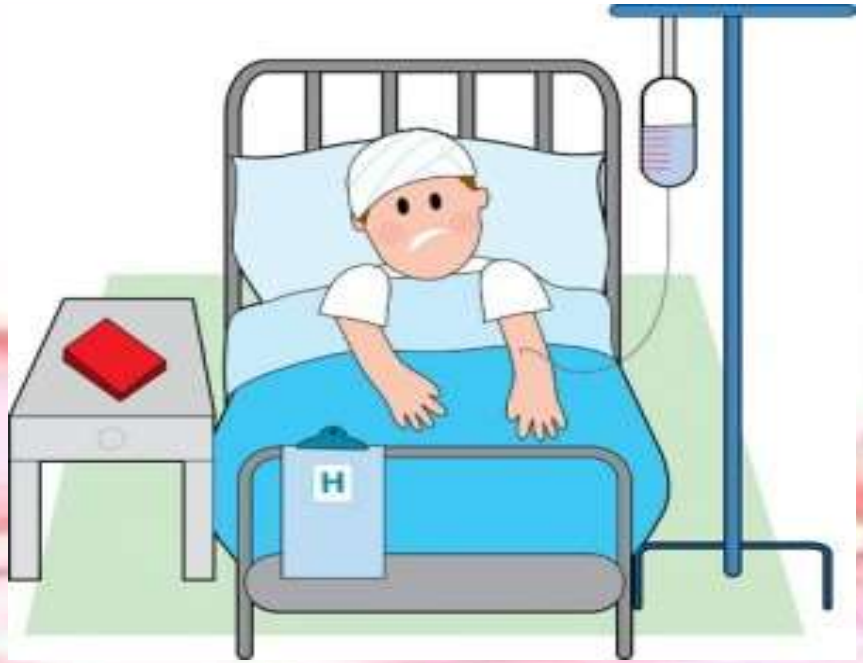
PATIENTS

Disadvantages

- Disease, other drugs, physiological changes may modify the drug absorption pattern.

Advantages

- *The patient will be benefited.*
- *Reflects the therapeutic efficacy of the drug.*
- *Drug absorption pattern in disease state can be evaluated.*
- *Avoids the ethical quandary of administering of drugs to a healthy subjects.*



SELECTION OF HUMAN VOLUNTEERS

(HEALTHY SUBJECTS)
As per FDA Regulations

- Adult healthy human of age 20-40, with uniform weight should be considered.
- For certain drugs female volunteers of age 20-40 can be selected.
- The volunteers selected should be clinically examined for any diseases.

- Volunteers **consent** must be obtained before involvement in testing.

- The volunteers should be **insured**.
- Volunteers must be advised to **abstain** from **any medication** for at least **one week**, and to **fast over night** prior to and for a minimum of **4hrs** after dosing.
- **A minimum of 10 half-lives** should be allowed for any two studies on the same subject.

- The human volunteers selected should be kept under **restricted dietary conditions** prior to **24hrs** of drug administration.

- The volunteers are **advised not** to undergo **vigorous physical exercise** during the testing

ESTIMATION / MEASUREMENT OF BIOAVAILABILITY

There are three methods to measure the bioavailability.

They are :

1) Pharmacokinetic methods
2) Pharmacodynamic methods
3) In vitro dissolution testing studies

- Pharmacokinetic methods and Pharmacodynamic methods are together called as in vivo methods.

- ***In vitro dissolution testing is the preliminary test carried on any dosage form for assessing rate and extent of drug release.***

Pharmacokinetic Method

(Indirect method of estimation)

1.Plasma concentration Vs time profile studies which includes

a) single dose studies

b) multiple dose studies

2. Urinary Excretion studies which includes

a) single dose studies

b) multiple dose studies

Pharmacodynamic Method

(Direct method of estimation)

It includes two methods :

1. Acute pharmacological studies
2. Pharmacotherapeutic / Clinical response studies

Typical Plasma Concentration time Profile

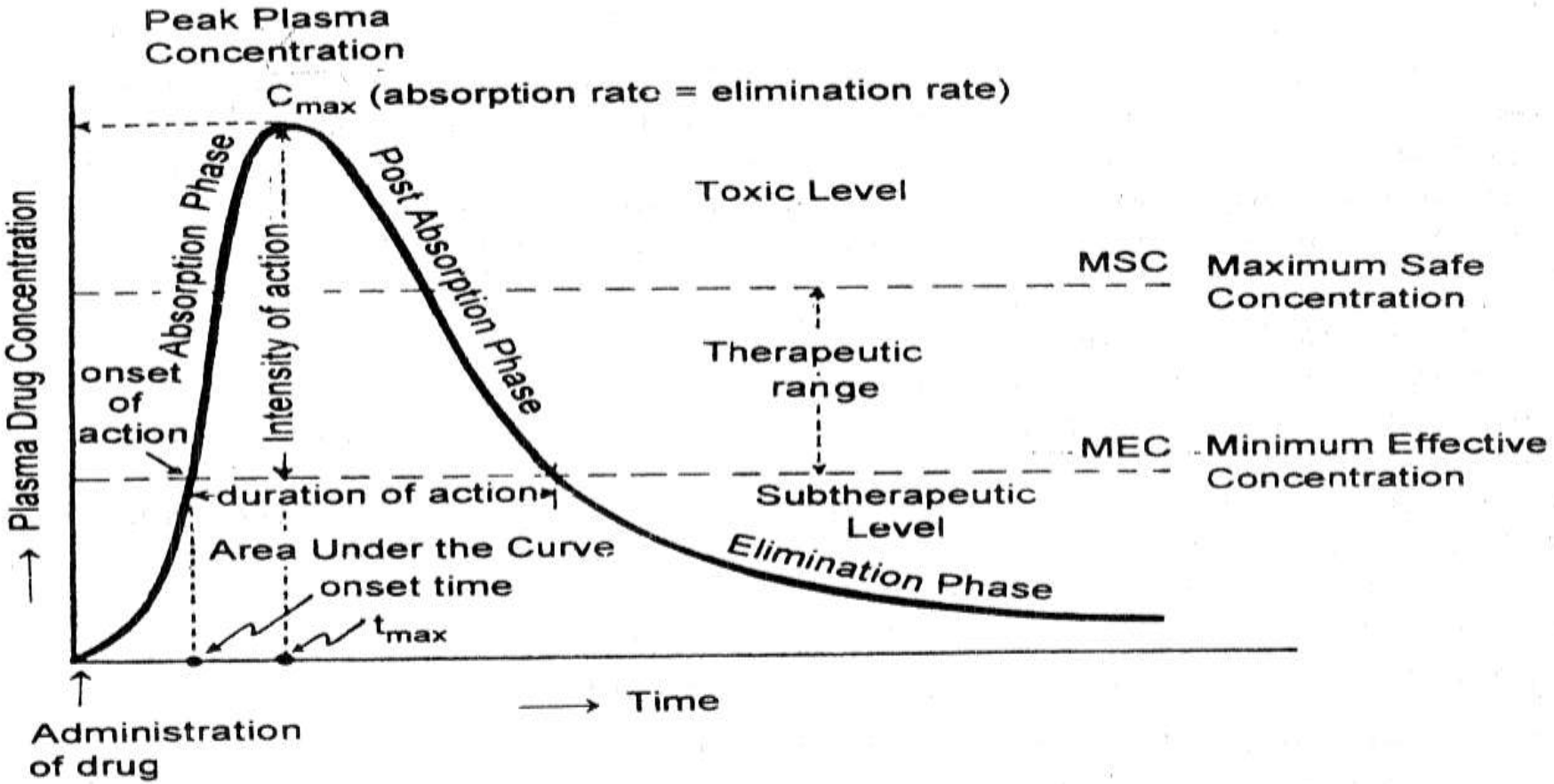


Fig. 9.1 A typical plasma concentration-time profile showing pharmacokinetic and pharmacodynamic parameters, obtained after oral administration of single dose of a drug.

SINGLE DOSE Vs MULTIPLE DOSE STUDIES

Single dose:-

Samples are withdrawn to the extent of 2-3 biological half lives.

- In one compartment model 3 samples are taken on descending curve and 3 samples on ascending curve.
- In multi compartment model 3 samples are taken on ascending curve and 5-6 samples on descending curve.

ADVANTAGES:

- They are easy.
- Offer less exposure to drugs.
- Less tedious.

DISADVANTAGES:

- Difficult to predict-steady state concentration.
- Lot of errors.
- Inter subject variability.
- More samples are required.

MULTIPLE DOSE STUDIES

- Samples are withdrawn to the extent of 5-6 biological half lives.

- Sample is withdrawn prior to the administration of next dose.

ADVANTAGES:

- More accurate.
- Steady state concentration is achieved.
- No. of subjects required is less.
- Inter subject variability is less.

DISADVANTAGES:

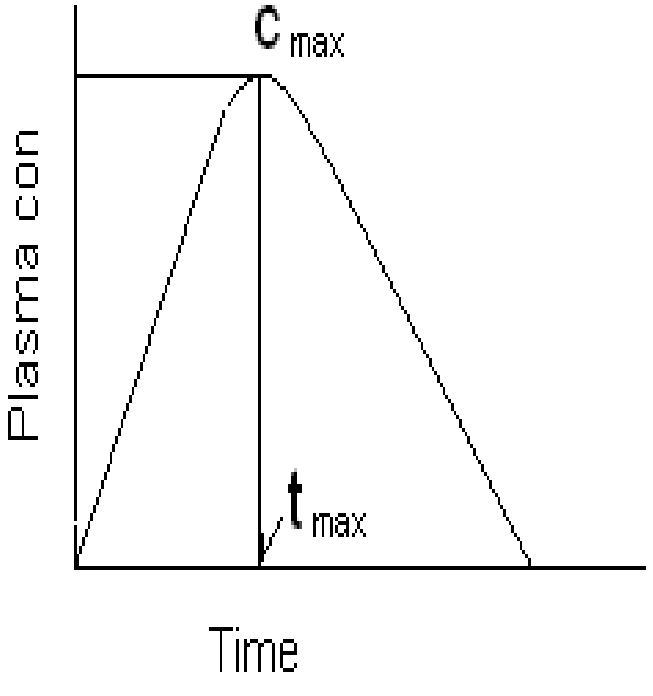
- Need expertise.
- Costly.
- Greater exposure to test drug. (adverse reactions)

PHARMACOKINETIC STUDIES

Plasma concentration Vs Time profile

Single dose

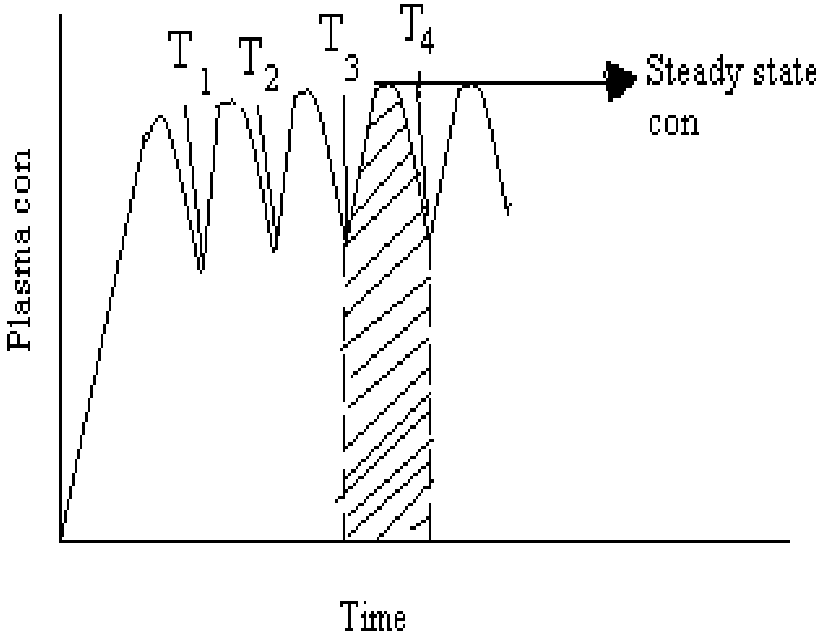
- From the graph **AUC, Tmax, and Cmax** were determined.



Multiple dose

- *Samples are withdrawn at stipulated time intervals after attaining the steady state concentration.*

$$Fr = \frac{[AUC]\ test\ D_{std}\ Ttest}{[AUC]std\ \ Dtest\ Tstd}$$



- *Bioavailability can be assessed by Cmax at steady state concentration.*

$$\mathbf{Fr= \frac{(Cmax\ ss)test\ Dstd\ Ttest}{(Cmax\ ss)std\ DtestTstandard}}$$

URINARY EXCRETION DATA

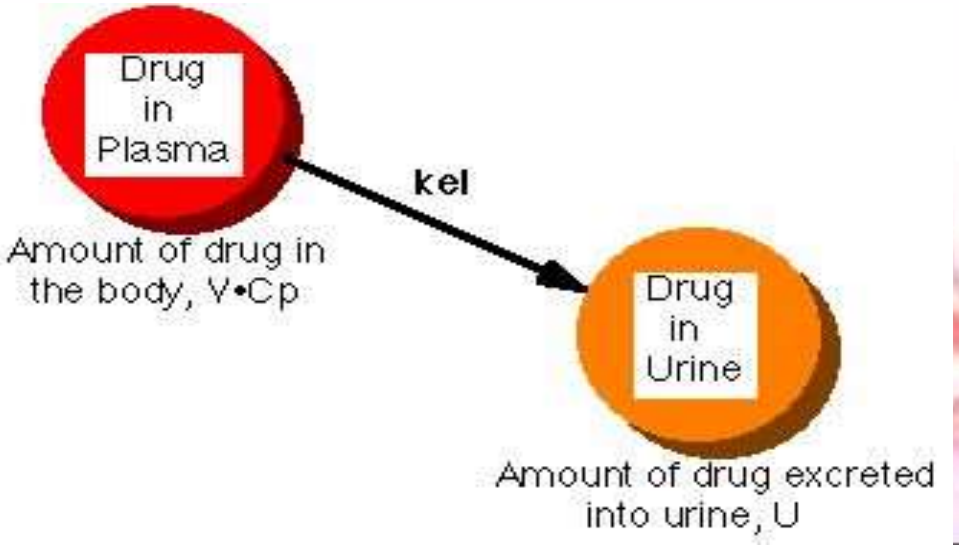
- Some of the drugs are excreted in unchanged form in urine.
- As a rule determination of bioavailability of urinary excretion data should be conducted only if at least 20% of administered dose is excreted unchanged in urine.

Ex : Thiazide diuretics and sulphonamides

- The 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.

CRITERIA TO OBTAIN VALID RESULTS

- At each sample collection total emptying of bladder is necessary to avoid errors resulting from addition of residual amount IN 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.

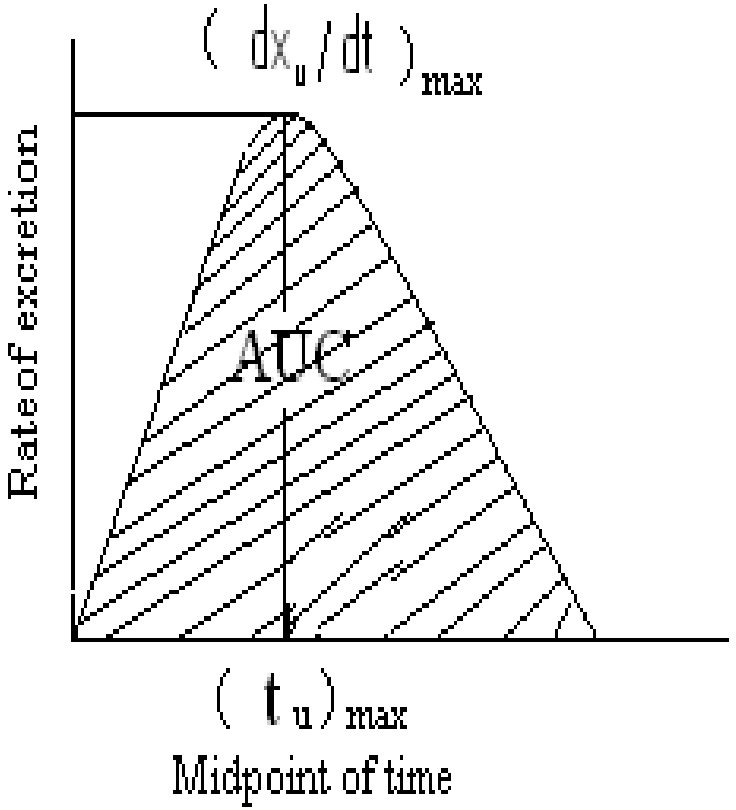


Three Parameters Examined In Single Dose Study

1. **The maximum urinary excretion rate (dXu/dt)max :** it is obtained from the peak of plot between rate of excretion Vs midpoint time of urine collection period. It is analogous to the Cmax .

2. **The time For maximum excretion rate (tu)max :** It is analogous to Tmax of plasma level data.

3. **The cumulative amount of drug excreted in the urine Xu~:** It is related to AUC of plasma level data.



- *The extent of bioavailability can be calculated by using*

$$F = \frac{(Xu)\text{oral Div}}{(Xu)\text{iv Doral}} \qquad Fr = \frac{(Xu)\text{test Dstd}}{(Xu)\text{std Dtest}}$$

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

$$Fr = \frac{(Xu, ss)\text{test Dstd Ttest}}{(Xu, ss)\text{std Dtest Tstd}}$$

PHARMACODYNAMIC STUDIES

- When bioavailability measurement by pharmacokinetic method is difficult , inaccurate or non reproducible, an acute pharmacological effect such as a change in ECG readings, pupil diameter etc is related to time course of related drug.
- Bioavailability can then be determined by construction of pharmacological effect-time curve as well as dose-response graphs.
- This method requires measurement of responses for at least 3 biological half lives of the drug in order to obtain a good estimate of AUC.

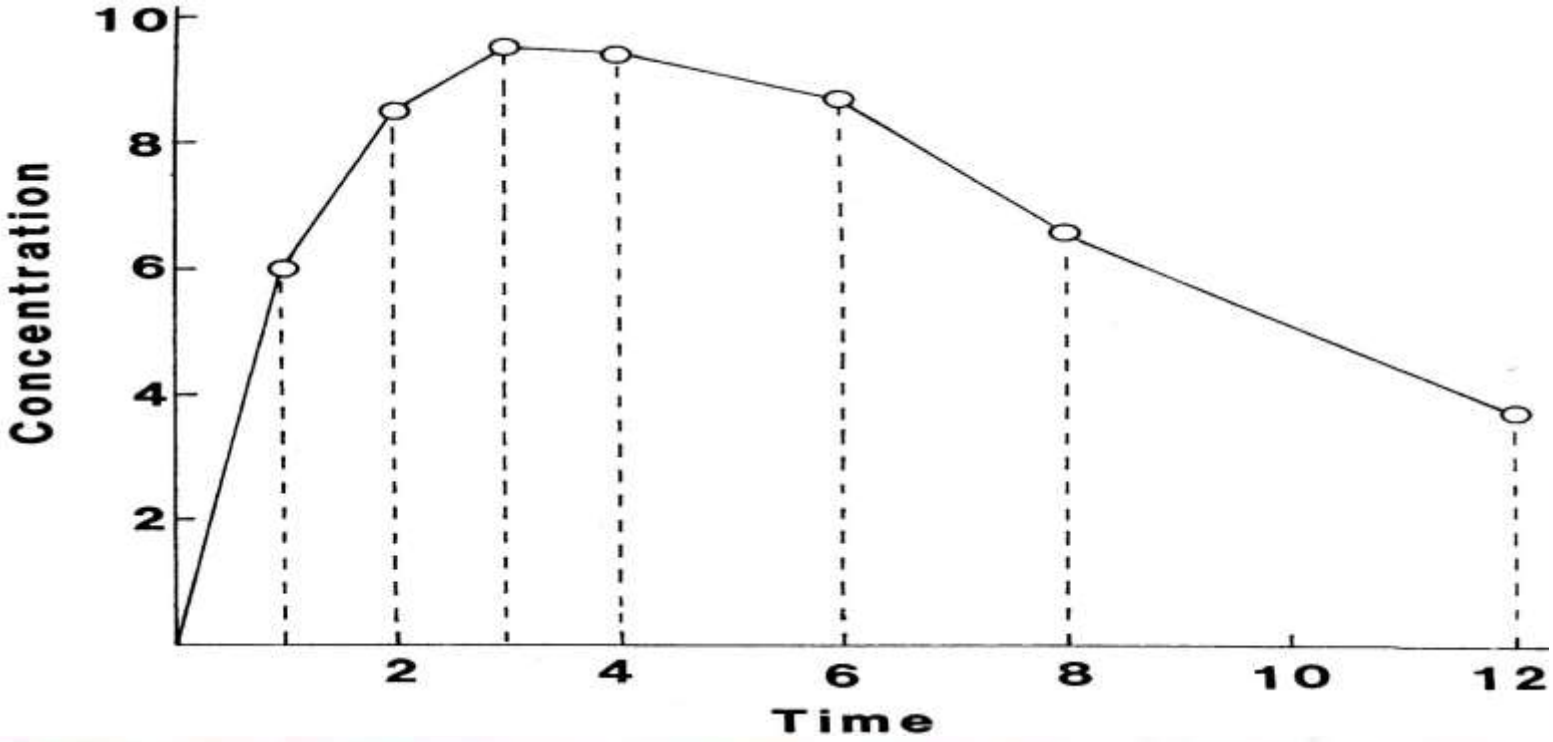
Dilation Of Pupil

THERAPEUTIC RESPONSE METHOD

- This method is based on observing the clinical response to a drug formulation given to patients suffering from disease for which it is intended to be used.

How Far It Is Cured ?????

ESTIMATION OF AREA UNDER THE CURVE



The area of trapezoids can be calculated by :

Area=1/2(C1+C2)(t2-t1)+

1/2(C2+C3)(t3-t2)…+

1/2(Cn-1+Cn)(t n – tn-1)

Example :

The area of 1st and 5th trapezoids can be calculated as:

Area (1)= ½(0+6.6)(1-0)=3.3µgm-hr/ml

Area (5)= ½ (9.4+8.7)(6-4)=18.10 µgm-hr/ml

Drug Concentration as a Function Of Time After Oral Administration

sample	Time	Concentration	Area (µgm-hr/ml)
1	0	0.0	3.30
2	1	6.6	7.55
3	2	8.5	9.00
4	3	9.5	9.45
5	4	9.4	18.10
6	6	8.7	15.30
7	8	6.6	20.60
8	12	3.7	_
		total	83.3

BIOEQUIVALENCE

EQUIVALENCE

It is a relative term that compares drug products with respect to a specific characteristic or function or to a defined set of standards.

CHEMICAL EQUIVALENCE

It indicates that two or more drug products contain the same labeled chemical substance as an active ingredient in the same amount.

PHARMACEUTICAL EQUIVALENCE

This term implies that two or more drug products are identical in strength, quality, purity, content uniformity and disintegration and dissolution characteristics; they may however differ in containing different excipients.

BIOEQUIVALENCE

It is a relative term which denotes that the drug substance in two or more identical dosage forms reaches the systematic circulation at the same relative rate and to the same relative extent i.e., their plasma concentration –time profiles will be identical without significant statistical differences.

THERAPEUTIC EQUIVALENCE

This term indicates that two or more drug products that contain the same therapeutically active ingredient, elicit identical pharmacologic effects and can control the disease to the same extent.

TESTING PROTOCOL FOR BIOAVAILABILITY AND BIOEQUIVALENCE STUDIES

Parallel Design:

- Two formulations are administered to two groups of volunteers.
- To avoid bias two formulations are administered randomly to the volunteers.

Disadvantages:

- inter-subject variation is not corrected.
- Inter-subject variation is greater than the variation between any formulations

PARALLEL DESIGN

- GROUP A

GROUP B

- **Standard** → **(SAME DOSE)** ← **Test**

6-10 biological half lives

obtain : Cmax,Tmax,AUC,etc…..

Cross Over Design:

- Each subject receives the test drug product and the reference drug product

- Minimizes the effect of inter-subject variability in the study

3 Types:-

- Latin Square crossover Design
- Balanced Incomplete Block Design (BIBD)
- Replicated crossover design

LATIN SQUARE CROSS OVER DESIGN

- Two square cross over (T+S)
- Three square cross over (S+2T)
- Four square cross square (S+3T)

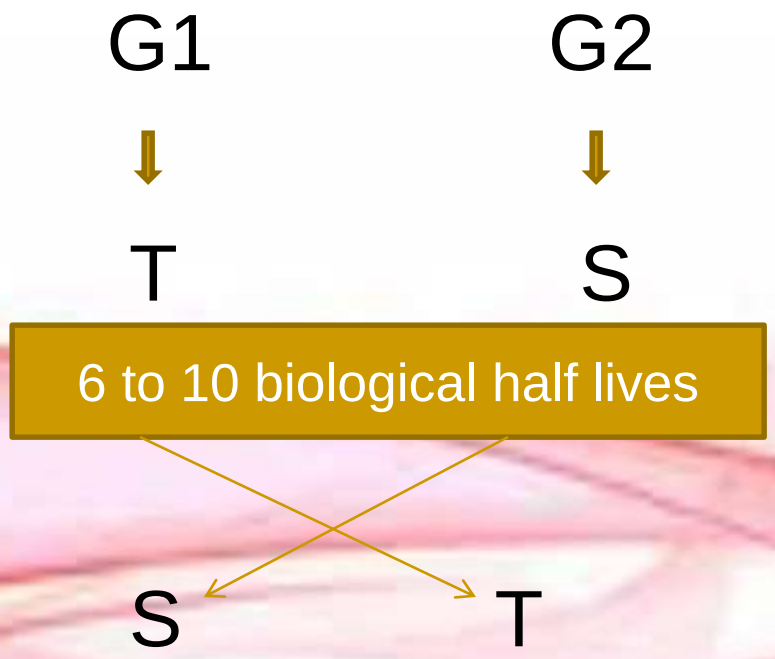
✓ Each subject receives each formulation only once.

✓ Each formulation is administered only once in each study period.

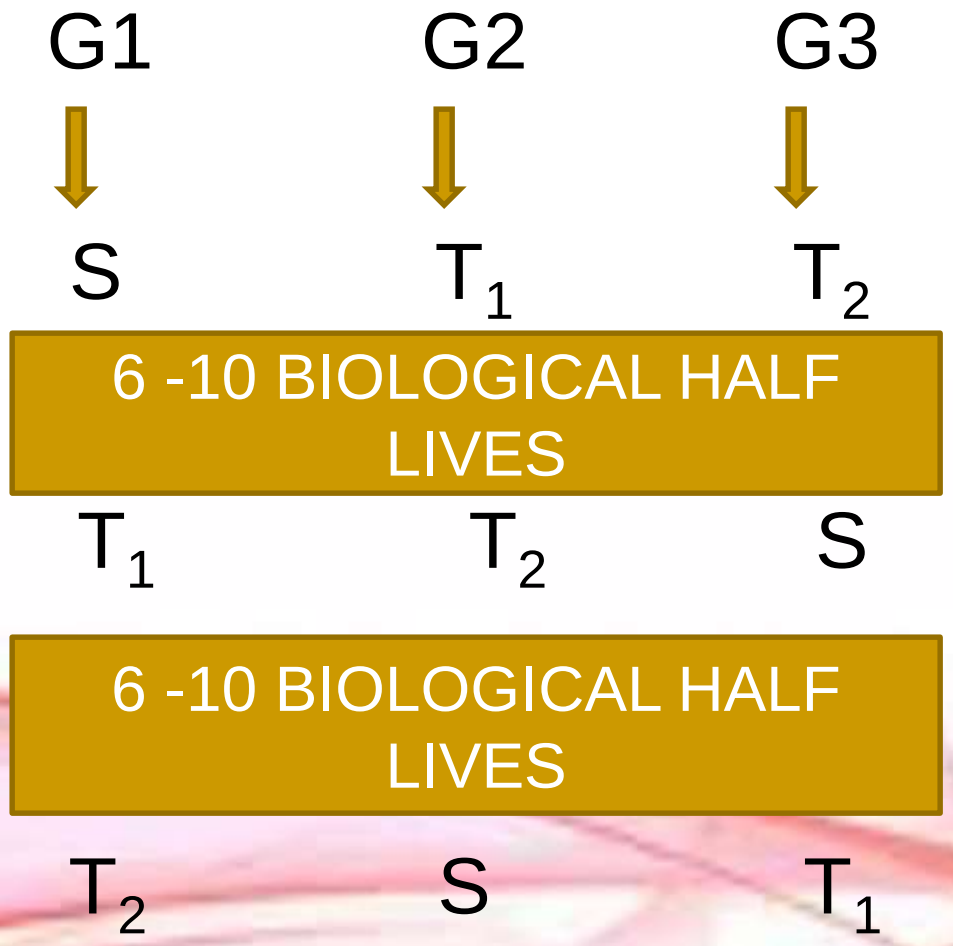
✓ Each subject acts as his own control.

LATIN SQUARE CROSS OVER DESIGN

- Two square cross over (T+S)

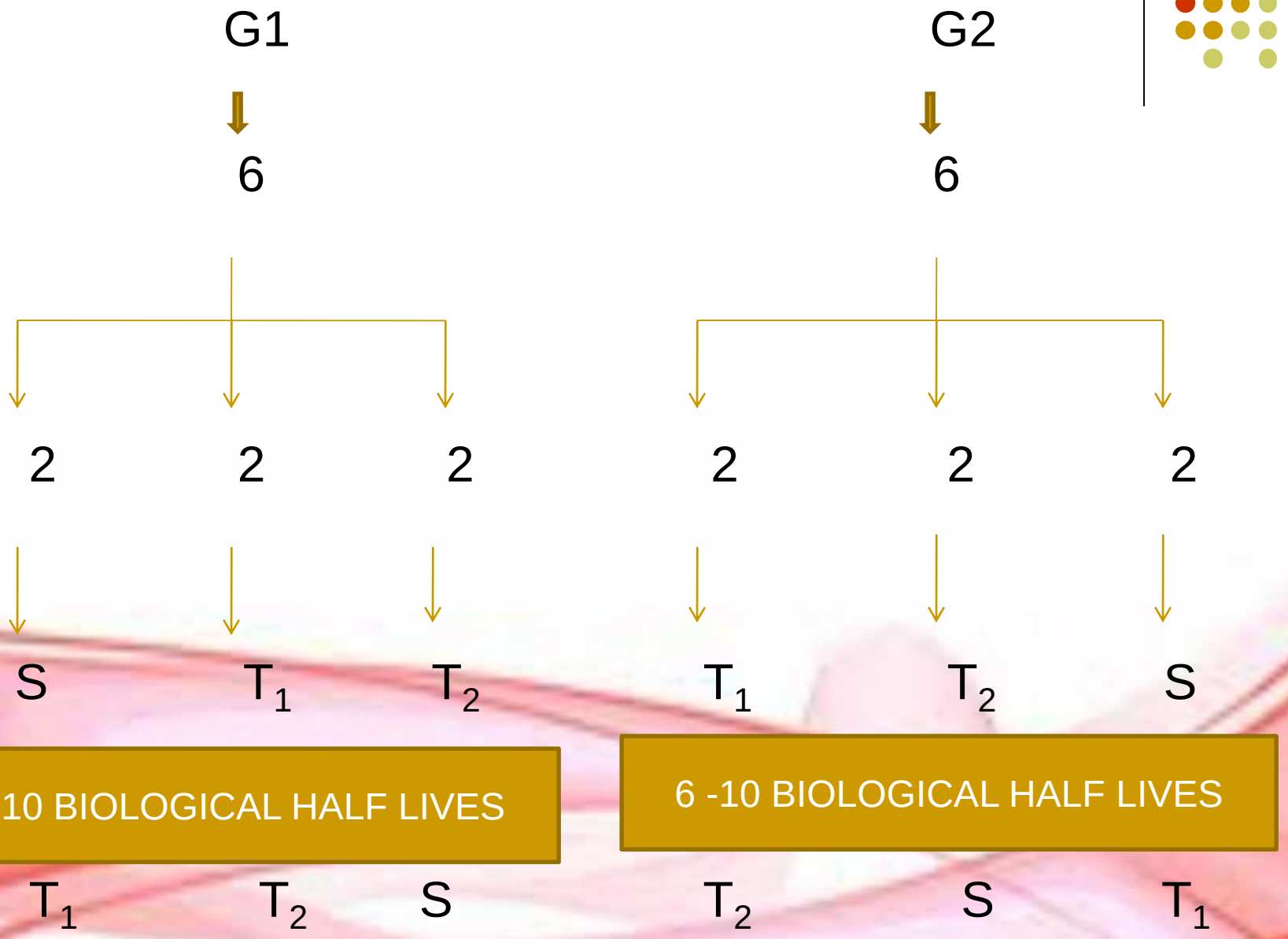


THREE SQUARE CROSS OVER DESIGN



Similarly four square cross over design is performed

Balanced Incomplete block Design



Balanced incomplete Block Design (BIBD) :

- Each subject receives not more than 2 formulations
- Each formulation is administered same number of times
- Each pair of formulations occurs together in the same number of subjects

Replicated crossover design :

- To determine individual bio-equivalence.
- To estimate within-subject variance for both the Test and Reference drug products.
- To estimate subject-by-formulation interaction variance.
- Reference-Reference and Test-Test comparisons may be made.

	Period 1	Period 2	Period 3	Period 4
Sequence 1	T	R	T	R
Sequence 2	R	T	R	T


Thank U