# BIOPHARMACEUTIC CONSIDERATIONS IN DRUG PRODUCT DESIGN AND IN VITRO DRUG PRODUCT PERFORMANCE

**M.Pharm 2nd SEM**
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# Contents:

- Introduction to Bioavailability.
- Methods of Assessing Bioavailability.

# Introduction

- A multi source drug product is a drug product that contains the same active drug substance in the same dosage form and is marketed by more than one pharmaceutical manufacturer.
- Single source drug products are drug products for which the patent has not expired or has certain exclusivities, so that only one manufacturer can make it. Single source drug products are usually brand name (Innovator) drug products.
- After the patent and other exclusivities for the brand-name drug expires, a pharmaceutical firm may manufacture a generic drug product that can be substituted for the branded drug product.

- Since the formulation and the method of manufacture of the drug product can affect the bioavailability and stability of the drug, the generic drug manufacturer must demonstrate that the generic drug product is bioequivalent and therapeutically equivalent to the brand name drug product.
- The therapeutic effectiveness of a drug depends upon the ability of the dosage form to deliver the medicament to its site of action at a rate and amount sufficient to elicit the desired pharmacological response.

# Definition

- **Bioavailability** is defined as the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action.
- For drug products that are not intended to be absorbed into the blood stream, bioavailability may be assessed by measurements intended to reflect the rate and extent to which the active ingredients or active moiety becomes available at the site of action.
- **Relative bioavailability** is the bioavailability of the drug from a drug product as compared to a recognized standard.
- **Absolute bioavailability** is, when the systemic availability of a drug after extra vascular administration is compared to IV dosing.

# Purpose of Bioavailability studies

- Bioavailability studies are performed for both approved active drug ingredients and therapeutic moieties not yet approved for marketing by the FDA.

- The drug products must meet all applicable standards of identity, strength, quality and purity. To ensure that these standards are met, the FDA requires Bioavailability or Pharmacokinetic studies for all drug products.

- Essential Pharmacokinetic parameters, including the rate and extent of systemic absorption, elimination half life and rates of excretion and metabolism should be established after single and multiple dose administration. Data from these in-vivo bioavailability studies are important to establish recommended dosage regimens and to support drug labeling.

- In-vivo bioavailability studies are also performed for new formulations of active drug ingredients or therapeutic moieties that are approved for marketing.

- The purpose of these studies is to determine the bioavailability and to characterize the pharmacokinetics of the new formulations or new dosage form. Bioavailability studies are used to define the effect of changes in the physicochemical properties of the drug substance and the effect of the drug product on the pharmacokinetics of the drug.

- Bioequivalence studies are also considered as performance measures of the drug product in-vivo.

# Objectives

Bioavailability studies are important in the:-

- Primary stages of development of a suitable dosage form for a new drug entity.
- Determination of influence of excipients, patient related factors and possible interactions with other drug on the efficacy of absorption.
- Development of new formulation of the existing drugs.
- 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.

## Factors influencing Drug absorption and Bioavailability;

The chain of events that occur following administration of a solid dosage form until its absorption into systemic circulation are as follows:

The process consists of four steps:-

- Disintegration of the drug product
- De-aggregation and subsequent release of the drug.
- Dissolution of the drug in the aqueous fluid at the absorption site.
- Movement of the dissolved drug through the GI membrane into systemic circulation and away from the absorption site.

- The rate at which the drug reaches the systemic circulation is determined by the slowest of the various steps involved in the sequence.
- Such a step is called as the rate determining or rate limiting step.

## Considerations in bioavailability study design:

- The area under the drug concentration-time curve (AUC) is used as the measure of the total amount of unaltered drug that reaches the systemic circulation.
- The AUC is depended on the total quantity of the available drug,$FD_0$ divided by the elimination rate constant,k, and the apparent volume of distribution,$V_D$ .F is the fraction of the dose absorbed. After IV administration F is equal to unity,because the entire dose enters the systemic circulation.
- Therefore the drug is considered to be completely available after IV administration. After oral administration of the drug,F may vary from a value of 0 (no drug absorption) to 1.(Complete drug absorption)

# Relative bioavailability

- It is the bioavailability of the drug from a drug product as compared to a recognized standard. Here the systemic availability of a drug after oral administration is compared with that of an oral standard of the same drug.
- The relative bioavailability of two drug products given at the same dosage levels and by the same route of administration can be obtained using the following equation;
- Relative Bioavailability = $\frac{[AUC]_A}{[AUC]_B}$
- Where drug product B is the recognized reference standard.
- This fraction maybe multiplied by 100 to give percent relative availability.
- It is used to characterize the absorption of a drug from its formulation.

# ABSOLUTE BIOAVAILABILITY:-

- When the systemic availability of a drug after extra vascular administration is compared to IV dosing, it is called Absolute bioavailability. It is generally measured by comparing the respective AUC's after extravascular and IV administration. Its determination is used to characterize a drug's inherent absorption properties from the EV site. Intravenous dose is selected as a standard because the drug is administered directly into the systemic circulation (100%Bioavailability) and avoids absorption step. Intramuscular dose can also be taken as a standard if the drug is poorly water soluble.
- Absolute Bioavailability after oral drug administration using plasma data can be determined as follows;
- Absolute Bioavailability=F= $\frac{[AUC]_{po}/dose_{po}}{[AUC]_{iv}/dose_{iv}}$
- It is denoted by F and is expressed as a fraction or as a percent by multiplying F x100

# Methods of assessing Bioavailability:-

The methods useful in quantitative evaluation of bioavailability can broadly divided into two categories;

- Pharmacokinetic methods
- Pharmacodynamic methods.

Clinical observations and in-vitro studies may also used to determine drug bioavailability from a drug product.

# PHARMACOKINETIC METHODS

These are very widely used and based on the assumption that the pharmacokinetic profile reflects the therapeutic effectiveness of a drug. Thus these are indirect methods.

The two major pharmacokinetic methods are

- Plasma level-time studies
- Urinary excretion studies.

# Plasma level-time studies.

- It is also called as Plasma drug concentration.
- It is the most reliable method and method of choice in comparison to urine data. It is a direct and objective way to determine systemic bioavailability.
- The method is based on the assumption that two dosage forms that exhibits super imposable plasma level-time profiles in a group of subjects should result in identical therapeutic activity.

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

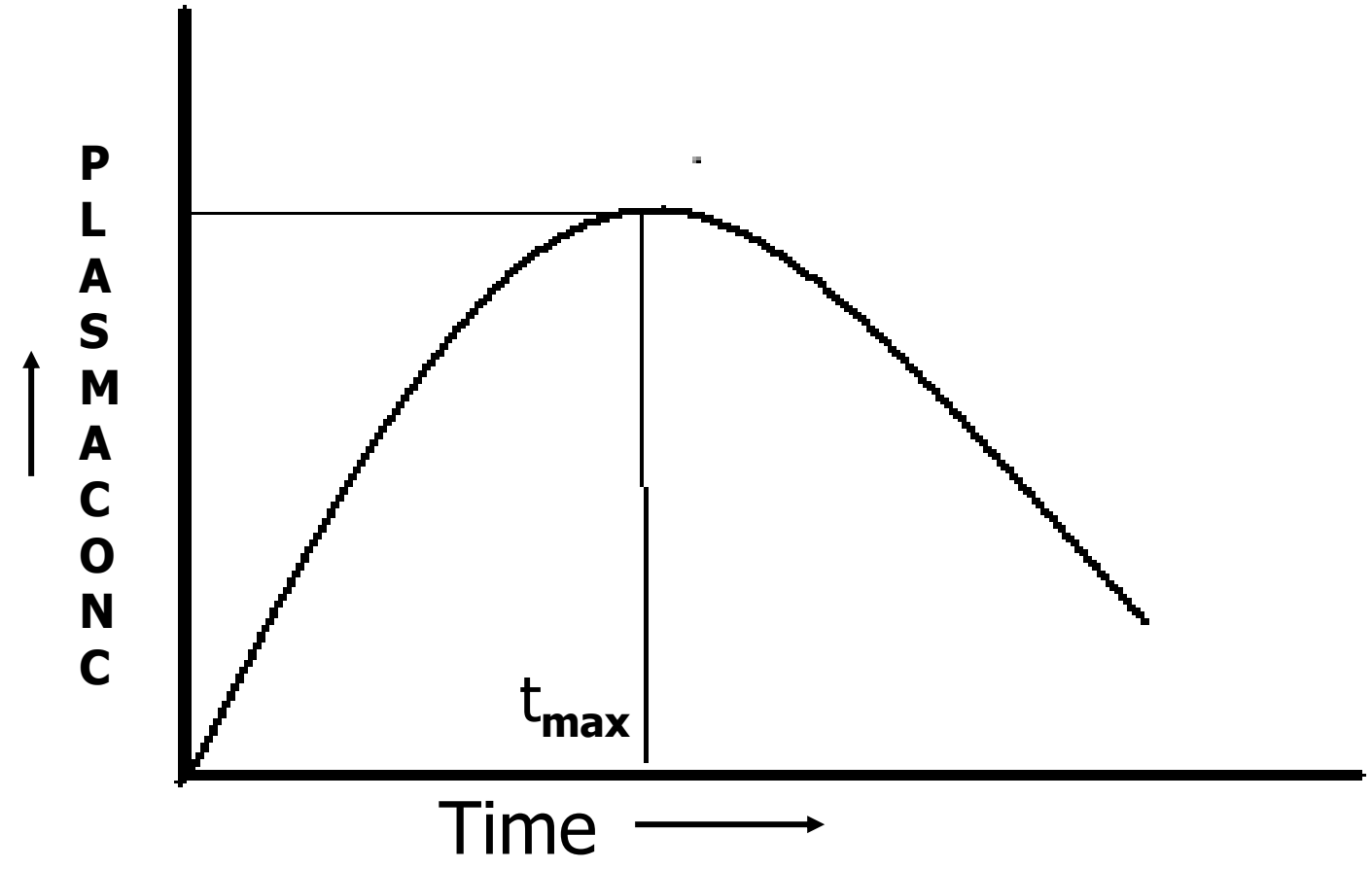
**$C_{max}$**

- The peak plasma drug concentration, $C_{max}$ represents the maximum plasma drug concentration obtained after oral administration. This gives an indication whether the drug is sufficiently absorbed systemically to provide a therapeutic response. In addition it provides warning of possible toxic levels of drugs. The units of $C_{max}$ are concentration units (eg;mg/ml, ng/ml)

**$t_{max}$**

- The peak time or time of peak plasma concentration, $t_{max}$ corresponds to the time required to reach maximum drug concentration after drug administration. It gives an indication of the rate of absorption. At $t_{max}$ peak drug absorption occurs and the rate of drug absorption exactly equals the rate of drug elimination.Units for $t_{max}$ are units of time (eg;hours,minutes)

# PLASMA DRUG LEVEL-TIME CURVE



## AUC

- The area under the plasma level –time curve, AUC is a measurement of the extent of drug bioavailability. It gives the measure of the extent of absorption or the amount of the drug that reaches the systemic circulation. The AUC is the area under the drug plasma level time curve from t=o to t=∞, and is equal to the amount of unchanged drug reaching the general circulation divided by the clearance.

$$[AUC]_o^{\infty} = \frac{FD_o}{\text{Clearance}} = \frac{FD_o}{kV_D}$$

Where F =fraction of dose absorbed

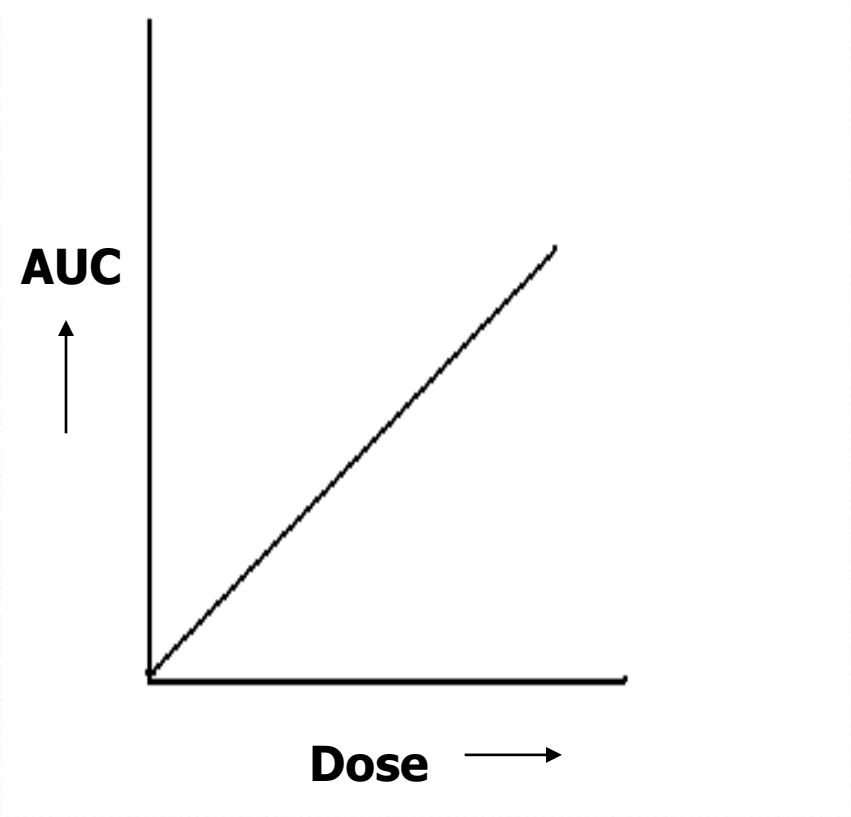
$D_o$ =Dose

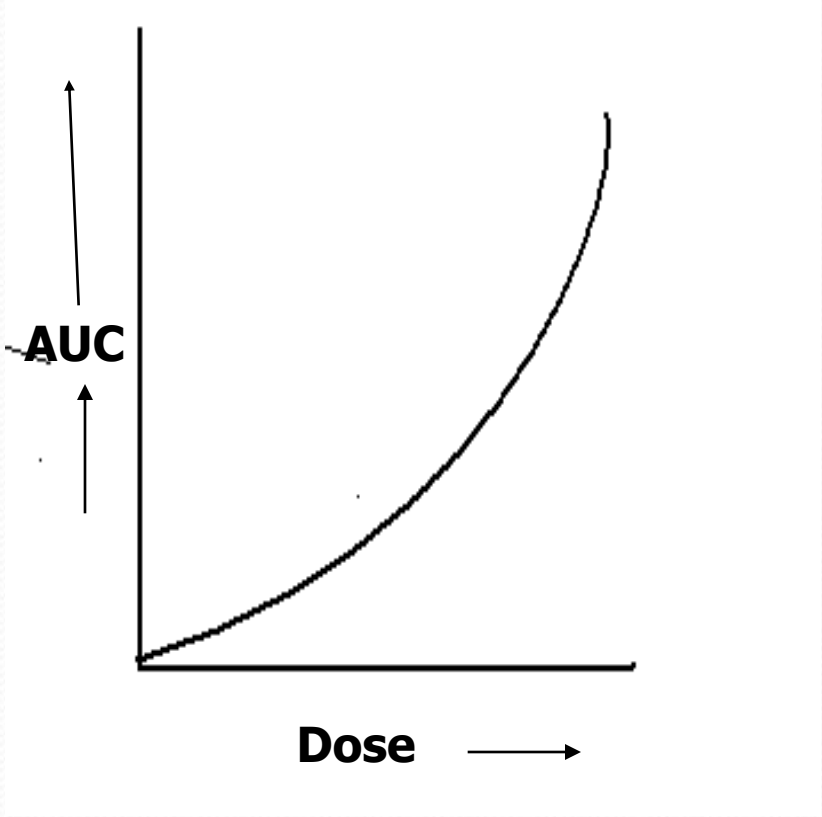
k =elimination rate constant

$V_D$ = Volume of distribution.

- The units of AUC are concentration time (eg;µg hr/ml)

# RELATIONSHIP BETWEEN AUC AND DOSE



The extent of bioavailability can be determined by the following equations;

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

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

Bioavailability can also be determined from the peak plasma concentration at steady state $C_{ss,max}$ according to the following equation.

$$Fr = \frac{(C_{ss,max})_{test}\ D_{std}\ i_{test}}{(C_{ss,max})_{std}\ D_{test}\ i_{std}}$$

# URINARY EXCRETION STUDIES

- It is an indirect method of estimating bioavailability.
- This method is based on the principle that the urinary excretion of the unchanged drug is directly proportional to the plasma concentration of drug. Thus even if a drug is excreted to some extent (atleast 10 to 20 %) in the urine bioavailability can be determined.
- Eg: Certain thiazide diuretics and sulphonamides have urine as the site of action, such as nitrofurantoin and hexamine.
- Timely urine samples must be collected and the total amount of urinary drug excretion must be obtained.

The 3 major parameters examined in urinary excretion data are ;

**$X_u$**

The cumulative amount of drug excreted in the urine, $X_u$ is related directly to the total amount of drug absorbed. It is also related to the AUC of plasma level data and increases as the extent of absorption increases.

Experimentally, urine samples are collected periodically after administration of a drug product. Each urine specimen is analyzed for free drug using a specific assay. A graph is constructed that relates the cumulative drug excreted to the collection time interval. When the drug is almost completely eliminated,(Point C), the plasma concentration approaches o and the maximum amount of drug excreted in the urine $X_u$ is obtained.

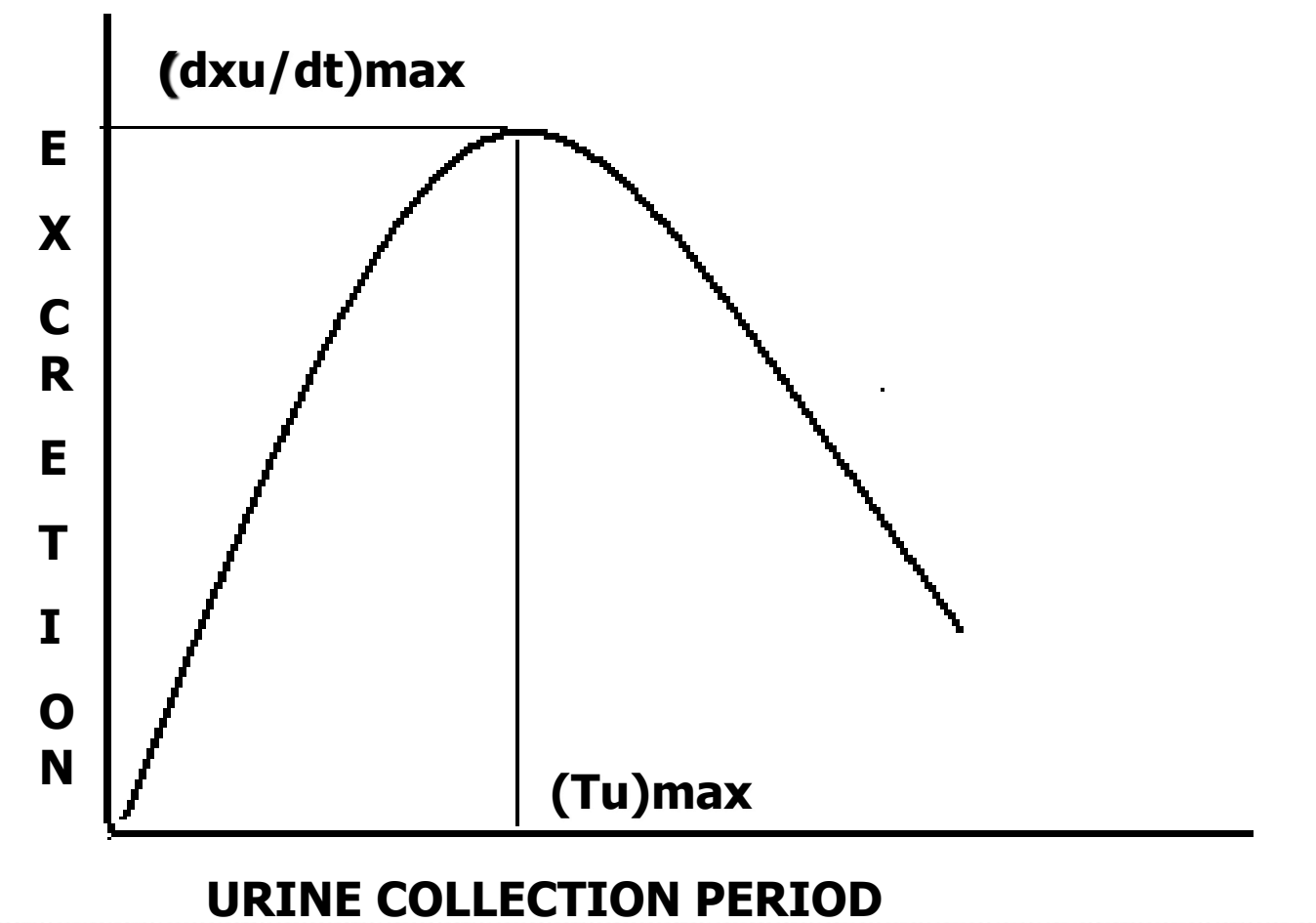
**$(dX_u/dt)_{max}$**

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 $C_{max}$ 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.

**$(t_u)_{max}$**

The time for maximum excretion rate, it is analogous to the $t_{max}$ of the plasma level data. Its value decreases as the absorption rate increases.

# URINARY EXCRETION STUDIES



The extent of bioavailability is calculated from the following equations;

$$F = \frac{(X_{u\infty})_{oral}\ D_{iv}}{(X_{u\infty})_{iv}\ D_{oral}}$$

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

$$Fr = \frac{(X_{u,ss})_{test}\ D_{std}\ f_{test}}{(X_{u,ss})_{std}\ D_{test}\ f_{std}}$$

$$Fr = \frac{(X_{u\infty})_{test}\ D_{std}}{(X_{u\infty})_{std}\ D_{test}}$$

Where($X_{u,ss}$) is the amount of drug excreted unchanged during a single dosing interval at the steady state.

# ADVANTAGES OF URINARY EXCRETION STUDIES

- This method is useful when there is a lack of sufficiently sensitive analytical technology to measure concentration of drugs in plasma with accuracy.
- Convenience of collecting urine samples.
- Direct measurement of absolute and relative bioavailablity is possible without the necessity of fitting the data to a mathematic model.
- When coupled with plasma level-time data,it can be used to estimate renal clearance of unchanged drug,by

  $CL_R$=total amount of drug excreted unchanged / AUC

# PHARMACODYNAMIC METHODS

- These methods are complimentary to pharmacokintetic approaches and involve direct measurement of drug effect on a physiological process as a function of time.

- The two pharmacodynamic methods involve determination of bioavailability from;

a)Acute pharmacodynamic effect/acute pharmacological response

b)Therapeutic response.

# ACUTE PHARMACODYNAMIC EFFECT

- When bioavailability measurement by pharmacokinetic methods is difficult,inaccurate or non reproducible,acute pharmacological effects such as change in ECG /EEG readings ,pupil diameter etc is related to the time course of a given drug.

- Bioavailabitlity can be then determined by construction of pharmacological effect –time curve as well as dose response graphs.It is measured over the period of time after administration of the drug product.The method requires measurement of responses for atleast 3 biological half lives of the drug in order to obtain a good estimate of AUC.

- The use of pharmcodynamic end points for the determination of bioavailability and bioequivalence is much more variable than the measurement of plasma or urine drug concentration.

## Disadvantage

- Pharmacological response tends to be more variable and accurate co-relation between measured response and drug available from the formulation is difficult.
- Moreover the observed response maybe due to an active metabolite whose concentration is not proportional to the concentration of parent drug responsible for pharmacological effect.

# THERAPEUTIC RESPONSE

- 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.

## Disadvantage

- Quantification of observed response is too improper to allow for reasonable assessment of relative bioavailability between two dosage forms of the same drug.

# References:


- Biopharmaceutics and Pharmacokinetics-A Treatise,By D M Brahmankar and Sunil B Jaiswal,Second edition,page no-315 to 325.
- Applied Biopharmaceutics and Pharmacokinetics by Shargel L ,Andrew B C ,5th Edition.page no-453 to 464

# THANK YOU