UNIT 5

BIOAVAILABILITY AND BIOEQIVALENCE

S. SANGEETHA, M.PHARM., (Ph.d)
Department of Pharmaceutics
SRM College of Pharmacy
SRM University
The bioavailability or systemic availability of an orally administered drug depends largely on the absorption and the extent of hepatic metabolism.

The bioavailability of an oral dosage form is determined by comparing the Area Under Curve (AUC) after oral administration of a single dose with that obtained when given IV.

Drug bioavailability = \( \frac{\text{AUC (oral)}}{\text{AUC (IV)}} \) = \( \frac{\text{Bioavailable dose}}{\text{Administered dose}} \)
DEFINITION
Bioavailability is defined as the rate and the absorption of drug that reaches the biological system in an active form, capable of exerting the desired pharmacological effect, including its onset, intensity and duration of its action.

THE NEED FOR BIOAVAILABILITY STUDIES

- Bioavailability studies provide an estimate of the fraction of the orally administered dose that is absorbed into the systemic circulation when compared to the bioavailability for a solution, suspension, or intravenous dosage form that is completely available.

- Bioavailability studies provide other useful information that is important to establish dosage regimen and to support drug labeling, such as distribution and elimination characteristics of the drug.

- Bioavailability studies provide information regarding the performance of the formulation.
**TYPES OF BIOAVAILABILITY**

- **Absolute bioavailability** – Absolute bioavailability of a drug in a formulation administered by an extravascular, including the oral route reaching the systemic circulation is the fraction of the same dose of the drug administered intravenously.

Absolute bioavailability = \( \frac{(AUC)_{abs}}{(AUC)_{iv}} \)

Absolute bioavailability = \( (AUC)_{abs} \times \text{Div} \)
\( (AUC)_{iv} \times \text{Dabs} \)

Where Dabs is the size of the single dose administered via the absorption site And Div is the dose size administered intravenously.
Relative bioavailability –
Relative bioavailability is a measure of the fraction of the given drug that is absorbed in the systemic circulation from a particular dose compared to a clinically proven standard dose of the same drug.

\[
\text{Relative bioavailability} = \frac{(\text{AUC})_{\text{test}}}{(\text{AUC})_{\text{STD}}} 
\]

\[
\text{Relative bioavailability} = (\text{AUC})_{\text{test}} \times \frac{D_{\text{std}}}{(\text{AUC})_{\text{std}} \times D_{\text{test}}}
\]
For assessing the bioavailability or clinical availability of a drug, its rate and extent of absorption and its first-pass metabolism must be evaluated.

These criteria are difficult or even impossible to quantify.

The method used to assess bioavailability depend upon the assumption that measurement of the drug concentration in a suitable body fluid, such as blood, plasma, serum, urine or sometime saliva, can be correlated with its clinical availability.

Bioavailability is determined by following methods

- **Pharmacokinetics method** – This method is more practical and discriminative. Pharmacokinetic methods are of two types.
  a) Determination of whole blood, plasma or serum concentration
  b) Urinary excretion method
a) The blood (or serum or plasma) concentration-time curve -

- Pharmacokinetics
  - what the body does to the drug
- Absorption
- Distribution
- Metabolism
- Elimination
Based on the plasma concentration-time curve, the following measurements are important for bioavailability studies.

- **MINIMUM EFFECTIVE PLASMA CONCENTRATION** - The minimum plasma concentration of the drug required to achieve a given pharmacological or therapeutic response. This value varies from drug to drug and from individual to individual as well as with the type and severity of the disease.

- **MAXIMUM SAFE CONCENTRATION** - The plasma concentration of the drug beyond which adverse effects are likely to happen.
**THERAPEUTIC RANGE** - The range of plasma drug concentration in which the desired response is achieved yet avoiding adverse effect. The aim is clinical practice is to maintain plasma drug concentration within the therapeutic range.

**ONSET OF ACTION** - On set of action is the time required to achieve the minimum effective plasma concentration following administration of drug formulation.

**DURATION OF ACTION** - Duration of action of the therapeutic effect of the drug is defined as the time period during which the plasma concentration of the drug exceeds the minimum effective level.

**INTENSITY OF ACTION** - In general, the difference between the peak plasma concentration and the minimum effective plasma concentration provides a relative measure of the intensity of the therapeutic response of the drug.
Peak concentration (Cmax) represents the highest concentration attained by the drug in the plasma. At this concentration, rate of drug input becomes equal to rate of drug output.

It is clear that formulation A should produce pain relief than formulation B, even though it seemed well absorbed, would not produce the desired pharmacological effect and would be ineffective in producing analgesia.
On the other hand, if the two curves represent blood concentrations following equal doses of two different formulations of the same cardiac glycoside.
An example can explain how difference in bioavailability of a given drug from different formulations marketed by various firm, can result in a patient being either over, under or correctly medicated.

Product D is more desirable form of a dosage form specially for drugs with narrow safety margin and relatively shorter half life.
b) **URINARY EXCRETION**

This method can be based if urinary excretion of unchanged drug is the main mechanism of elimination of the drug.

Bioavailability can be calculated as follows,

$$F = \frac{(D_{u\infty})}{f}$$

- **F** = Fraction of the dose absorbed
- **Du∞** = cumulative amount of drug excreted in the urine
- **f** = fraction of unchanged drug excreted in the urine

5x the elimination ½ life = time at which the drug is “completely” (97%) eliminated from the body:

- 1x ½ life - 50% of the original drug removed
- 2x ½ life - 75%
- 3x ½ life - 87.5%
- 4x ½ life - 93.75%
- 5x ½ life - 96.875%
LIMITATION

- There is a high degree of variability.
- Urinary data are valid only if the excretion of the drug or metabolite is related to the bioavailable dose of the drug.
- Urinary data cannot be reliably used to determine bioequivalence, Cmax, Tmax, absorption rate and duration.
2) FROM DISSOLUTION STUDIES

- In vitro dissolution studies are used to assess the product quality.
- In vitro dissolution rate should correlate with in vivo bioavailability.
- A dosage form with a rapid dissolution rate is likely to have a rapid rate of drug bioavailability in vivo.
- Bioavailability is not dependent on the dissolution of the drug product, but also on the permeability and solubility of the drug substance.
FACTORS AFFECTING BIOAVAILABILITY

There are three major absorption factors

1. The dose of drug administered, i.e. the blood level will rise and fall in Proportion to the dose administered.
2) The same as the first but brought about by a different process, of drug absorbed from a given dosage form. The effect of only one half of the drug absorbed from a dosage form is equivalent to lowering the dose.
3) The rate of absorption of the drug, if absorption from the dosage form is more rapid than the rate of absorption then toxic level can be exceeded. If absorption from the dosage form is sufficiently slow minimum effective level cannot be attained.
THE OTHER FACTORS ARE AS FOLLOWS

PHYSIOLOGICAL FACTORS

• Gastrointestinal fluids (pH, bile salts, complexing agent)
• Motility (gastric emptying, presence of food, rest and exercise)
• Absorption surface (physiological integrity, area and blood flow)

- **Surface area**
  - small intestine = 200 m²
  - stomach = 1 m²

- **Permeability**
  - intestinal membrane > stomach

- **Blood flow** (for perfusion rate-limited absorption)
  - small intestine = 1000 mL/min through intestinal capillaries
  - stomach = 150 mL/min

- **Gastric emptying and pH**

- **GI transit**
  - Rate of gastric emptying is a controlling step for rapid absorption
PHYSICO-CHEMICAL FACTORS

• Lipid and water solubility
• Partition coefficient
• Dissociation constant
• Polymorphic form
• Surface area
• Particle size
• Crystal shape
• Stability

PHARMACOLOGICAL FACTOR

• Variation in drug content
• Storage (drug and excipient stability)
• State of drug (particle size, polymorphism)
**ROTATING BASKET (APPARATUS I) DISSOLUTION TESTING MODEL**

| APPARATUS                          | APPRATUS 1: ROTATING BASKET FOR CAPSULES  
|                                   | APPRATUS 2: PADDLE FOR TABLETS          |
| ROTATION SPEED                    | 100 rpm (BASKET)  
|                                   | 50-75 rpm (PADDLE)                      |
| TEMPERATURE                       | 37 ± 0.5°C                                 |
| UNITS TO BE TESTED                | 12                                         |
| DISSOLUTION MEDIA                 | 900 ml OF AQUEOUS MEDIA OF VARIOUS pH     |
| SAMPLING SCHEDULE                 | 1, 2, 4 HRS AND EVERY 2 HRS THEREAFTER UNTILL 80% OF THE DRUG IS RELEASED |
| TOLERANCE                         | AS ESTABLISHED                            |
ROTATING PADDLE (APPARATUS 2)

fig 2 Paddle stirring element
INTRODUCTION

Both bioavailability and bioequivalence focus on measuring the absorption of the drug into systemic circulation.

Bioavailability is a comparison of the drug product to an IV formulation, a solution or a suspension, whereas bioequivalence is a comparison with predetermined bioequivalence limits.

The bioequivalence is said to exist when the bioavailability of a drug with different formulation is the same.
**DEFINITION**

**Equivalence** – Equivalence is more relative term that compares one drug product with another or with a set of established standards. Equivalence may be defined in several ways:

**Chemical equivalence** indicates that two or more dosage forms contain the labelled quantities of drug.

**Clinical equivalence** occurs when the same drug from two or more dosage forms gives identical in vivo effects as measured by a pharmacological response or by control of a symptom or a disease.

**Therapeutic equivalence** implies that one structurally different chemical can yield the same clinical result as another chemical.

**Bioequivalence** indicates that drug in two or more similar dosage forms reaches the general circulation at the same relative rate and the same relative extent.
NEED FOR BIOEQUIVALENCE

• Bioequivalence studies provide a link between the pivotal and early clinical trial formulation.

• Bioequivalence studies are for determination of the therapeutic equivalence between the pharmaceutical equivalence generic drug product and a corresponding reference listed drug.

• Bioequivalence studies provide information on product quality and performance when there are changes in components, composition and method of manufacture after approval of the drug product.
A COMMON PITFALL: CROSS – STUDY COMPARASION

- Most common error made in bioavailability data is that of cross – Study comparison.
- This occurs when the blood concentration – time curve of a drug product in one study is compared with the blood concentration – time curve of that drug product in another study.
- There are three reasons:
  - **Different Subject Population:**
  - **Different Study Condition:**
  - **DIFFERENT ASSAY METHODOLOGY**
Different Subject Population:

ASC-31%
AUC-21%

PEAK & AREA -5%

ASC-8%
AUC-9%

ASC-31%
AUC-21%

fig 1 average serum conc of phenoxyethyl penicillin foll oral administration of 500mg given as 1 tablet of std or test.

fig 2 avg serum conc of phenoxyethyl penicillin foll oral administration of 500mg given as 1 tablet of recognised std or test product.

fig 3 avg serum conc of phenoxyethyl penicillin foll a single oral dosage form of recognised std in two different subject population.
Different Study Condition:

- Two 250mg erythromycin tablets. No film or enteric coating.
- Two 250mg erythromycin tablet film coated
- Two 250mg erythromycin tablet enteric coated

Fig. 4 avg serum erythromycin conc administered in 500mg doses as three different tablet dosage forms.

Fig. 5 avg serum erythromycin conc administered in 500mg doses as three different tablet dosage forms.
DIFFERENT ASSAY METHODOLOGY

avg plasma prednisolone levels foll 60mg of prednisone administered to 24 normal adults as a single oral dose of twelve 5mg prednisone tablets from two different manufacturers. plasma levels were determined by a competitive protein-binding assay.

avg plasma prednisolone levels foll 60mg of prednisone administered to 24 normal adults as a single oral dose of twelve 5mg prednisone tablets from two different manufacturers. plasma levels were determined by a radioimmunoassay procedure. Figs
Fig 9: avg plasma prednisolone profiles administered as a single 60 mg dose to 24 normal adults. Plasma levels were determined by both a competitive protein binding assay and a radioimmunoassay.
LIMITATION OF BIOAVAILABILITY AND BIOEQUIVALENCE

- A cross over design may be difficult for drugs with a long elimination half life.
- Highly variable drugs may require a far greater number of subjects to meet the FDA bioequivalence characteristics.
- Certain characteristics in the biotransformation of drugs make it difficult to evaluate the bioequivalence of such drugs. For e.g. for drugs that are stereoisomer with a different rate of biotransformation and a different pharmacodynamic response, the measurement of individual isomers may be difficult for analytical reasons.
- Drugs that are administered by routes other than the oral route drugs/dosage forms that are intended for local effects have minimal systemic bioavailability. E.g. ophthalmic, dermal, intranasal and inhalation drug products.