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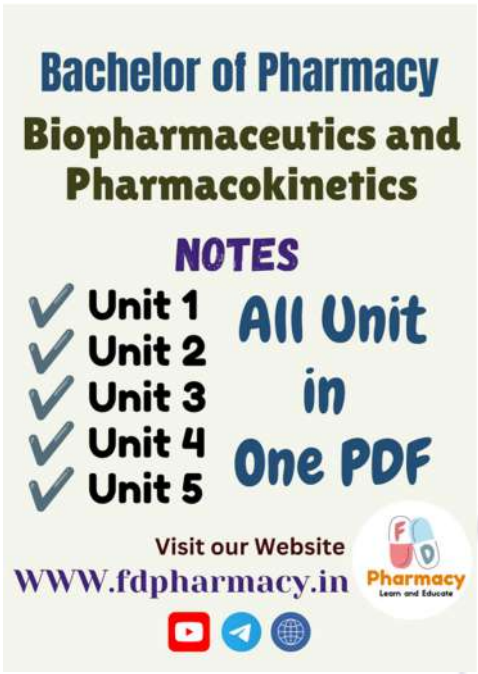
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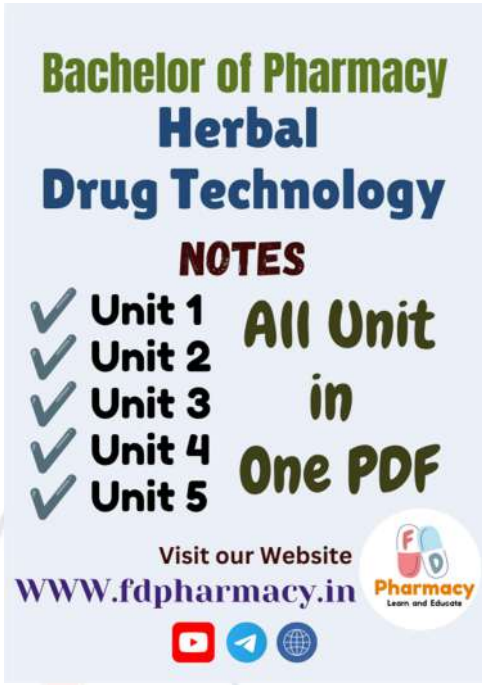
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BIOPHARMACEUTICS AND PHARMACOKINETICS

UNIT 2

TOPIC :

- **Bioavailability and Bioequivalence :** Definition and Objectives of bioavailability, absolute and relative bioavailability, measurement of bioavailability, in-vitro drug dissolution models, in-vitro-in-vivo correlations, bioequivalence studies, methods to enhance the dissolution rates and bioavailability of poorly soluble drugs.

Bioavailability and Bioequivalence

Bioavailability and bioequivalence are important concepts in biopharmaceutics and pharmacokinetics. They help in understanding how much drug reaches systemic circulation and how effectively different formulations of the same drug perform in the body.

These concepts are essential in:

- Dosage form design
- Drug development
- Generic drug approval
- Therapeutic effectiveness

Bioavailability

Bioavailability is defined as:

"The rate and extent to which an active drug ingredient reaches systemic circulation in unchanged form."

It indicates:

- How much drug is absorbed
- How fast drug reaches blood circulation

Objectives of Bioavailability

The main objectives are:

1. To determine rate and extent of drug absorption
2. To compare different dosage forms
3. To study effect of formulation on absorption
4. To evaluate therapeutic effectiveness of drugs
5. To develop safe and effective dosage forms
6. To determine proper dose and dosing interval
7. To compare generic and branded products

Factors Affecting Bioavailability

Pharmaceutical Factors

- Dosage form
- Particle size
- Disintegration time
- Dissolution rate
- Excipients used

Physiological Factors

- Gastric emptying time
- GI pH
- Blood flow
- Intestinal motility
- Food intake

Drug Related Factors

- Solubility
- Stability
- Lipid solubility
- First pass metabolism
- Protein binding

Types of Bioavailability

There are mainly two types:

1. Absolute Bioavailability
2. Relative Bioavailability

1. Absolute Bioavailability

Absolute bioavailability compares the bioavailability of a drug from a non-intravenous dosage form with intravenous administration.

IV route is considered standard because:

- Drug directly enters systemic circulation
- Bioavailability of IV administration is 100%

Formula

$$F = \frac{AUC_{oral}}{AUC_{IV}} \times \frac{Dose_{IV}}{Dose_{oral}} \times 100$$

Where:

- F = Absolute bioavailability
- AUC = Area under plasma concentration-time curve

Importance

- Measures fraction of administered drug reaching circulation
- Helps evaluate oral absorption
- Determines first pass effect

Example

If oral bioavailability of a drug is 50%, only half of administered dose reaches systemic circulation.

2. Relative Bioavailability

→ Relative bioavailability compares bioavailability of one formulation of a drug with another formulation of same drug.
→ One formulation acts as reference product.

Formula

$$F_{relative} = \frac{AUC_{test}}{AUC_{reference}} \times \frac{Dose_{reference}}{Dose_{test}} \times 100$$

Importance

- Compares generic and branded formulations
- Helps formulation development
- Evaluates changes in manufacturing process

Bioequivalence

Bioequivalence refers to the absence of significant difference in the rate and extent of absorption of two pharmaceutical equivalents when administered at same molar dose under similar conditions.

Pharmaceutical Equivalents

Two products are pharmaceutical equivalents if they contain:

- Same active ingredient
- Same dosage form
- Same strength
- Same route of administration

Objectives of Bioequivalence

1. To compare generic and innovator products
2. To ensure therapeutic equivalence
3. To confirm safety and efficacy
4. To maintain product quality
5. To obtain regulatory approval

Measurement of Bioavailability

Measurement of bioavailability is the process of determining:

- The rate of drug absorption
- The extent of drug absorption into systemic circulation

It helps evaluate the performance of a dosage form and ensures therapeutic effectiveness of the drug.

Bioavailability is mainly measured using:

- Pharmacokinetic methods
- Pharmacodynamic methods
- Clinical methods
- In-vitro methods

Objectives of Measurement of Bioavailability

1. To determine rate and extent of drug absorption
2. To compare different dosage forms
3. To evaluate therapeutic effectiveness
4. To compare generic and branded products
5. To study effect of formulation factors
6. To ensure consistent drug action

Methods of Measuring Bioavailability

1. Pharmacokinetic Methods

⇨ This is the most commonly used method.
⇨ In this method:
  - Drug concentration in plasma, blood or urine is measured at different time intervals after administration.

⇨ The obtained data is used to determine bioavailability parameters.

Important Pharmacokinetic Parameters

AUC (Area Under Curve)

→ AUC represents the total amount of drug absorbed into systemic circulation.
→ Higher AUC indicates greater bioavailability.
→ The plasma concentration-time graph is used to calculate AUC.

Cmax

Cmax is the maximum plasma concentration of drug achieved after administration.
It indicates:

- Rate of absorption
- Intensity of drug action

Tmax

Tmax is the time required to reach maximum plasma concentration.
It indicates:

- Speed of absorption

Smaller Tmax means faster absorption.

Plasma Concentration-Time Curve

A graph is plotted between:

- Plasma drug concentration
- Time

The area under this curve represents bioavailability.

$$y = \text{Plasma Drug Concentration},\ x = \text{Time}$$

Determination of Absolute Bioavailability

→ Absolute bioavailability compares oral administration with IV administration.
→ IV administration is considered 100% bioavailable.

Formula

$$F = \frac{AUC_{oral}}{AUC_{IV}} \times \frac{Dose_{IV}}{Dose_{oral}} \times 100$$

Where:

- F = Bioavailability
- AUC = Area under curve

Determination of Relative Bioavailability

→ Relative bioavailability compares one formulation with another formulation of same drug.

Formula

$$F_{relative} = \frac{AUC_{test}}{AUC_{\quad}} \times \frac{Dose_{reference}}{Dose_{\quad}} \times 100$$

2. Pharmacodynamic Methods

→ In this method, bioavailability is measured by observing pharmacological response produced by drug.

→ Used when plasma concentration measurement is difficult.

Examples

- Blood pressure reduction
- Heart rate changes
- Bronchodilation

Advantages

- Useful when drug assay is difficult

Disadvantages

- Less accurate
- Biological response may vary

3. Clinical Methods

→ Bioavailability is measured using clinical response in patients.

Examples

- Relief from pain
- Reduction in fever
- Improvement in symptoms

Advantages

- Measures actual therapeutic effect

Disadvantages

- Time consuming
- Expensive
- Less precise

4. Urinary Excretion Method

→ Some drugs are excreted unchanged in urine.

→ Bioavailability can be estimated by measuring:

  - Amount of unchanged drug excreted in urine

In-Vitro Drug Dissolution Methods

→ In-vitro drug dissolution methods are laboratory techniques used to measure:
  - How quickly a drug dissolves
  - How much drug dissolves

→ from its dosage form such as tablets or capsules into a dissolution medium outside the body (in-vitro).

→ These methods simulate conditions of the human gastrointestinal tract and help predict drug behavior in the body (in-vivo).

Objectives of In-Vitro Dissolution Testing

1. To ensure uniform drug release from batch to batch
2. To predict bioavailability and bioequivalence
3. To evaluate quality of dosage forms
4. To support formulation development
5. To detect manufacturing variations
6. To ensure therapeutic effectiveness

Principle of Dissolution Testing

When a dosage form comes in contact with dissolution medium:

- Drug dissolves gradually into solution
- Dissolved drug becomes available for absorption

The dissolution rate depends upon:

- Surface area
- Solubility
- Agitation
- Temperature
- Particle size

Ideal Requirements of Dissolution Test

- Simulate GI tract conditions
- Maintain constant temperature
- Provide proper agitation
- Ensure reproducible results
- Maintain sink conditions

USP Dissolution Apparatus

The United States Pharmacopeia (USP) has developed different dissolution apparatus for testing various dosage forms.

Main USP dissolution methods include:

1. USP Apparatus I – Basket Method
2. USP Apparatus II – Paddle Method
3. USP Apparatus III – Reciprocating Cylinder Method
4. USP Apparatus IV – Flow Through Cell Method
5. USP Apparatus V, VI and VII

1. USP Apparatus I – Basket Method

Principle

→ The dosage form is placed inside a rotating basket which is immersed in dissolution medium.

→ The basket rotates at a constant speed allowing drug dissolution.

Construction

- Cylindrical vessel
- Stainless steel basket
- Rotating shaft
- Temperature control system

Working

- Dissolution medium is maintained at 37 ± 0.5°C
- Basket rotates at specified speed
- Samples are withdrawn at regular intervals

Applications

- Capsules
- Floating dosage forms
- Delayed release products

Advantages

- Prevents floating of capsules
- Uniform agitation

Disadvantages

- Basket clogging may occur
- Not suitable for sticky formulations

2. USP Apparatus II – Paddle Method

Principle

→ A paddle rotates in the dissolution medium while the dosage form rests at the bottom of the vessel.

→ Drug dissolves due to agitation created by paddle movement.

Construction

Consists of:

- Cylindrical vessel
- Paddle attached to rotating shaft
- Temperature control system

Working

- Medium maintained at 37 ± 0.5°C
- Paddle rotates at constant speed
- Samples collected periodically

Applications

Most commonly used for:

- Tablets
- Capsules
- Immediate release dosage forms

Advantages

- Simple and economical
- Easy operation
- Widely accepted

Disadvantages

- Floating dosage forms may create problems
- Hydrodynamic variations possible

3. USP Apparatus III – Reciprocating Cylinder Method

Principle

→ The dosage form moves up and down in dissolution medium between different compartments.
→ This simulates gastrointestinal movement.

Construction

Contains:

- Reciprocating cylinders
- Multiple dissolution vessels
- Motor-driven system

Applications

Suitable for:

- Controlled release formulations
- Extended release products

Advantages

- Simulates GI conditions better
- Useful for modified release systems

Disadvantages

- Expensive equipment
- Complex operation

4. USP Apparatus IV – Flow Through Cell Method

Principle

Dissolution medium continuously flows through a cell containing the dosage form.

Fresh medium maintains sink conditions.

Construction

Consists of:

- Flow-through cell
- Pump system
- Reservoir
- Heating system

Applications

Suitable for:

- Poorly soluble drugs
- Modified release dosage forms
- Powders and implants

Advantages

- Continuous fresh medium supply
- Better sink conditions
- Useful for poorly soluble drugs

Disadvantages

- Costly apparatus
- Complex setup

5. USP Apparatus V – Paddle Over Disc Method

Applications

Mainly used for:

- Transdermal patches

In this method:

- Patch is attached to disc
- Paddle rotates above disc

6. USP Apparatus VI – Cylinder Method

Used mainly for:

- Transdermal delivery systems

Patch is attached to rotating cylinder.

7. USP Apparatus VII – Reciprocating Holder Method

Used for:

- Chewable tablets
- Transdermal systems
- Non-disintegrating dosage forms

The dosage form moves repeatedly in dissolution medium.

IN-VITRO IN-VIVO Correlation (IVIVC)

In-Vitro In-Vivo Correlation (IVIVC) is a predictive mathematical relationship between:

- In-vitro drug dissolution or release
  and
- In-vivo drug absorption or bioavailability.

In simple words, IVIVC predicts how a drug product will behave inside the human body based on laboratory dissolution studies.

Objectives of IVIVC

1. To predict in-vivo drug absorption from in-vitro dissolution data
2. To reduce the need for repeated human studies
3. To support formulation development
4. To help in bioequivalence studies
5. To establish dissolution specifications
6. To support regulatory approval of formulations

Importance of IVIVC

IVIVC is important because it:

- Predicts drug performance in the body using laboratory tests
- Reduces expensive and time-consuming clinical studies
- Helps formulation optimization
- Supports scale-up and manufacturing changes
- Useful for modified release dosage forms
- Helps maintain product quality and consistency

Basic Principle of IVIVC

If the rate of drug dissolution in laboratory conditions reflects the rate of drug absorption in the body, then a correlation exists between:

- In-vitro dissolution
  and
- In-vivo absorption

A good IVIVC means:

- Faster dissolution → Faster absorption
- Slower dissolution → Slower absorption

Levels of IVIVC (According To FDA)

The FDA classifies IVIVC into different levels:

1. Level A Correlation
2. Level B Correlation
3. Level C Correlation
4. Multiple Level C Correlation

1. Level A Correlation

Level A correlation is a point-to-point relationship between:

- In-vitro dissolution
  and
- In-vivo absorption.

It is the strongest and most preferred form of IVIVC.

Characteristics

- Direct relationship at every time point
- Most accurate correlation
- Predicts complete plasma concentration-time profile

Example

- 30% drug dissolves in vitro in 1 hour
  and
- 30% drug is absorbed in vivo in 1 hour, then a Level A correlation exists.

Advantages

- Highly predictive
- Useful for regulatory approval

Applications

Mostly used for:

- Sustained release formulations
- Controlled release dosage forms

2. Level B Correlation

Level B correlation compares:

- Mean in-vitro dissolution time
  with
- Mean in-vivo residence or absorption time.

It uses statistical moment analysis.

Characteristics

- Not a point-to-point relationship
- Less predictive than Level A

Advantages

- Easier to develop

Limitations

- Cannot predict plasma concentration profile accurately
- Limited regulatory usefulness

3. Level C Correlation

Level C correlation relates:

- One dissolution parameter
  with
- One pharmacokinetic parameter.

Example

- Drug dissolved at 60 minutes
  compared with:
- Cmax or AUC

Characteristics

- Simple correlation
- Weak predictive ability

Advantages

- Easy to establish

Limitations

- Not reliable for complete prediction
- Limited usefulness

4. Multiple Level C Correlation

Multiple Level C correlation uses:

- Multiple dissolution time points
  and
- Multiple pharmacokinetic parameters.

It is better than single Level C correlation.

Characteristics

- More informative than Level C
- Still less powerful than Level A

Example of IVIVC

Suppose a sustained release tablet:

- Releases 50% drug in 2 hours in-vitro
  and
- 50% drug is absorbed in 2 hours in-vivo.

If this relationship continues for other time points also, then a Level A IVIVC exists.

Bioequivalence Studies

Bioequivalence means that two drug products show similar bioavailability and produce the same therapeutic effect in the body.

Usually, bioequivalence studies compare:

- Brand (innovator) drug
  and
- Generic drug

Two products are considered bioequivalent when:

- They release the same amount of active drug
- At the same rate
- And produce similar therapeutic effects and safety profiles.

Bioequivalence Refers To Similarity In:

1. Rate of Absorption

How fast the drug enters systemic circulation.

2. Extent of Absorption

How much drug reaches systemic circulation.

Importance of Bioequivalence

Bioequivalence studies are important because they:

- Ensure therapeutic equivalence
- Confirm safety and efficacy of generic products
- Support regulatory approval
- Reduce cost of medicines
- Ensure batch-to-batch consistency

Need of Bioequivalence Studies

1. Approval of generic drugs
2. Comparison of different formulations
3. Ensuring same therapeutic effect
4. Detecting formulation differences
5. Quality control and regulatory compliance

Parameters Used in Bioequivalence Studies

1. Cmax

Cmax is the maximum plasma concentration achieved by the drug.

It indicates:

- Rate of absorption

2. Tmax

Tmax is the time required to reach maximum plasma concentration.

It indicates:

- Speed of absorption

3. AUC (Area Under Curve)

AUC represents total drug exposure in the body.

It indicates:

- Extent of absorption

Plasma Concentration-Time Curve

Bioequivalence is evaluated using plasma concentration versus time profile.

$$y = \text{Plasma Drug Concentration},\ x = \text{Time}$$

Example of Bioequivalence

If:

- Brand A 500 mg tablet
  and
- Generic B 500 mg tablet

show:

- Same Cmax
- Similar Tmax
- Similar AUC

then both products are considered bioequivalent.

Conditions For Bioequivalence

Two formulations are considered bioequivalent if:

- Their absorption profiles are similar
- No significant difference exists in rate and extent of absorption

Usually tested in:

- Healthy volunteers
- Crossover studies

Biopharmaceutical Classification System (BCS)

BCS stands for Biopharmaceutical Classification System.

It classifies drugs based on:

- Solubility
- Intestinal permeability

BCS helps predict:

- Drug absorption
- Bioavailability
- Suitability for formulation development

BCS Classification

Class	Solubility	Permeability	Absorption	Examples
I	High	High	Good	Metoprolol
II	Low	High	Variable	Ibuprofen, Phenytoin
III	High	Low	Poor permeability	Cimetidine, Acyclovir
IV	Low	Low	Poor	Furosemide

Class I Drugs

Characteristics

- High solubility
- High permeability
- Rapidly absorbed
- Good bioavailability

Example

- Metoprolol

Class II Drugs

Characteristics

- Low solubility
- High permeability
- Dissolution is rate-limiting step

Importance

Bioavailability can be improved by enhancing solubility.

Suitable for:

- Controlled release formulations

Examples

- Ketoconazole
- Ibuprofen
- Phenytoin

Class III Drugs

Characteristics

- High solubility
- Low permeability

Absorption depends on:

- GI membrane integrity
- Food effects
- Drug interactions

Examples

- Cimetidine
- Atenolol
- Acyclovir

Class IV Drugs

Characteristics

- Low solubility
- Low permeability
- Poor absorption and bioavailability

Challenges

- Difficult formulation development
- Require novel drug delivery systems

Example

- Furosemide

Methods to Enhance Dissolution Rate and Bioavailability of Poorly Soluble Drugs

Poorly soluble drugs often show poor absorption and low therapeutic effect. Various methods are used to improve their dissolution and bioavailability.

1. Particle Size Reduction

Principle

Reducing particle size increases surface area and dissolution rate.

According to Noyes–Whitney equation:

$$\frac{dC}{dt} = \frac{DA(Cs-C)}{h}$$

Increasing surface area increases dissolution rate.

Techniques

- Micronization
- Nanonization
- Ball milling
- High pressure homogenization

Advantages

- Simple method
- Effective for BCS Class II drugs

Limitations

- Aggregation
- Poor flow properties

2. Solid Dispersions

Principle

Drug is dispersed in water-soluble carrier to improve:

- Wettability
- Solubility
- Dissolution rate

Types

- Eutectic mixtures
- Solid solutions
- Amorphous dispersions

Carriers Used

- PEG
- PVP
- HPMC

Advantages

- Increased dissolution
- Improved bioavailability

Limitations

- Stability problems
- Difficult large-scale production

3. Use of Surfactants

Principle

Surfactants reduce surface tension and improve wetting and solubilization.

Examples

- Sodium Lauryl Sulfate (SLS)
- Tween 80
- Poloxamers

Advantages

- Improved dissolution
- Enhanced bioavailability

Limitations

- High concentration may cause GI irritation

4. Salt Formation

Principle

Conversion of drug into salt form increases aqueous solubility.

Requirements

Drug must contain ionizable groups.

Example

- Aspirin sodium salt

Limitations

- Stability issues
- Not suitable for all drugs

5. Solid Lipid Nanoparticles (SLNs)

Principle

Drug is incorporated into lipid nanoparticles.

Advantages

- Controlled drug release
- Improved bioavailability
- Better stability

Applications

Useful for:

- Lipophilic drugs

6. Nanostructured Lipid Carriers (NLCs)

Improved form of SLNs with better drug loading and stability.

7. Use of Co-solvents

Co-solvents improve solubility of poorly soluble drugs.

Examples

- Ethanol
- Propylene glycol

8. Complexation

Drug forms soluble complex with another compound.

Example

- Cyclodextrin complexes

9. pH Adjustment

Changing pH improves solubility of weak acids and weak bases.

10. Prodrug Formation

Drug chemically modified into more absorbable form.