BIOPHARMACEUTICS

UNIT 2 NOTES

ELIMINATION

- DRUG METABOLISM
- FACTORS AFFECTING EXCRETION
- NON RENAL ROUTE

BIOAVAILABILITY

- ABSOLUTE & RELATIVE
- MEASUREMENT OF BT
- BIOEQUIVALENCE STUDIES

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ELIMINATION

Elimination is the process by which a drug is removed from the systemic circulation either unchanged or after being metabolized, resulting in the termination of its pharmacological effects.

COMPONENTS OF ELIMINATION

① The two major components of Elimination are :
② Metabolism (Biotransformation)
Excretion.

ⓘ **Metabolism**
- It occurs mainly in liver.
- Also known as Biotransformation.
- It is the process by which Active drug is converted into excreted form.

ⓘⓘ **Excretion**
- It mainly occurs in kidneys.
- It is the process by which drug & its metabolites are removed from the body.

METABOLISM

- It is also known as 'Biotransformation'.
- It is a process by which body transforms a drug into more readily excretable forms.
- The primary site for metabolism is Liver.
- Other sites include kidney, intestines, lungs and plasma
- Metabolism usually involves enzymatic reactions in the liver that alter (changes) the chemical structure of drug.
- These reactions makes the drug more water soluble and thus drugs becomes easier to be eliminated from the body via urine or bile.
- The metabolism of a drug usually converts:
  - Lipid Soluble → Water Soluble
  - Unionised → Ionized
- Metabolism is crucial for drug's duration and intensity of action, as well as for its overall safety profile.

DRUG METABOLISM

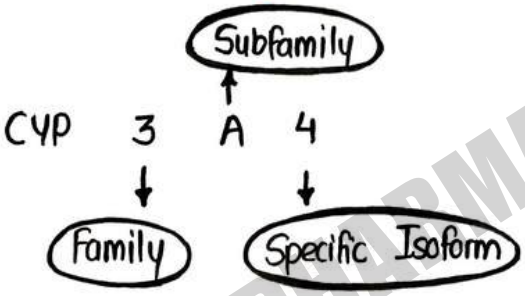
Metabolism usually leads to conversion of:

- Active Drug → Active Metabolite
- Active Drug → Inactive Metabolite
- Inactive Drug → Active Metabolite

Cytochrome P450 Enzymes

- Cytochrome P450 enzymes are group of proteins in the body that help breakdown drugs, toxins and other substances
- In Cytochrome P450, P stands for pigment that has maximum light absorption at wavelength 450 nm.
- Several families of CYP enzymes are involved in metabolism of drugs.
- These are named as CYP followed by a number (denotes family), then alphabet (subfamily) and again a number (specific isoform of the enzyme)

Example :



- CYP 3A4 forms the maximum hepatic content (26%) of CYP enzymes and is involved in metabolism of maximum percentage of drugs (33%).

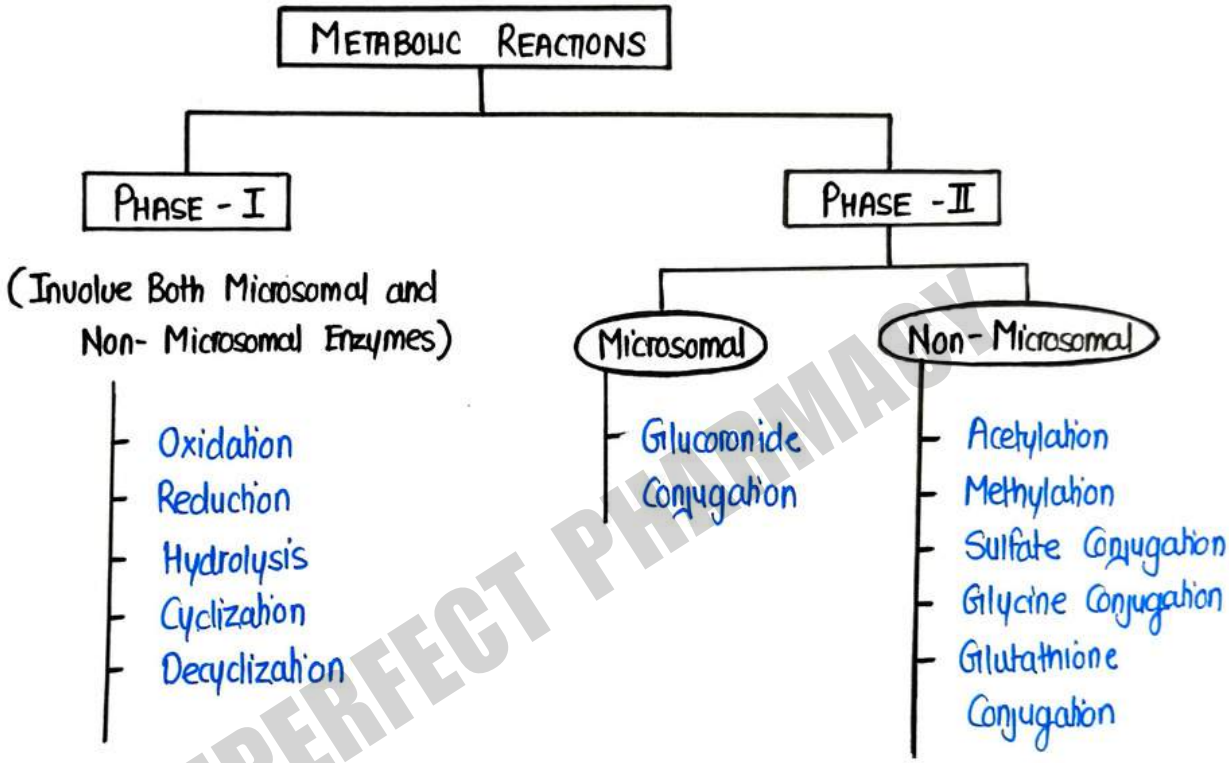
Example Of CYP Enzymes

- CYP3A4
- CYP2D6
- CYP2C19
- CYP2C9
- CYP1A2

Types Of Metabolism Reaction

There are mainly two types of Biotransformation reactions :

- Phase I Reaction
- Phase II Reaction



① Phase - I Reactions

These reactions introduce functional groups in the drug. It includes :

- Oxidation
- Reduction
- Hydrolysis
- Cyclization
- Decyclization

ⓐ Oxidation

- Oxidation is the process of addition of oxygen to a drug molecule or removal of hydrogen from a drug molecule.
- Oxidation is primarily mediated by enzymes like CYP450s and results in the formation of more polar metabolites, which can be easily excreted from the body.
- Example : Phenytoin, Phenobarbitone, Propranolol

ⓑ Reduction

- Reduction is the process of addition of Hydrogen or removal of Oxygen from a drug molecule.
- It is less common than Oxidation.
- Example : Chloramphenicol, Warfarin etc.

ⓒ Hydrolysis

- Breakdown of drug molecule by addition of water is known as Hydrolysis.
- This is common among esters and amides.
- It is mediated by enzymes such as esterase, amidases & pephidases.

ⓓ Cyclization

- In this, straight chain compound converted into ring structure.
- example : Cycloguanil from Proguanil

ⓔ Decyclization

- It involves opening up of ring structure of cyclic drug molecule.
- Example : Barbiturates.

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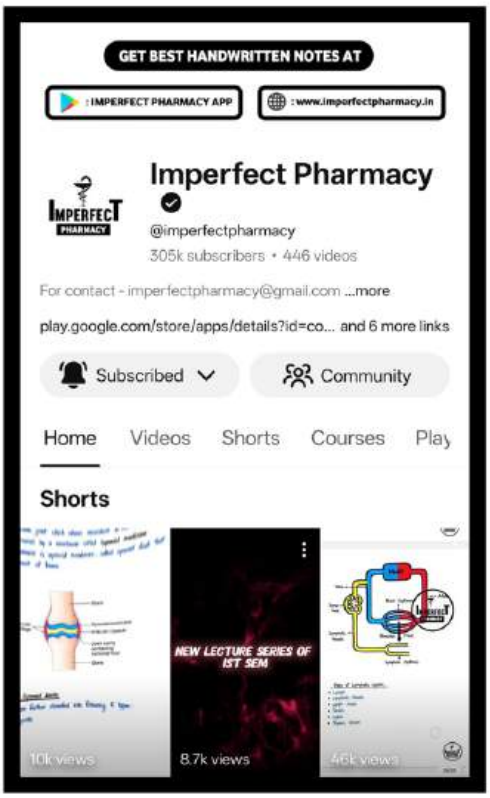

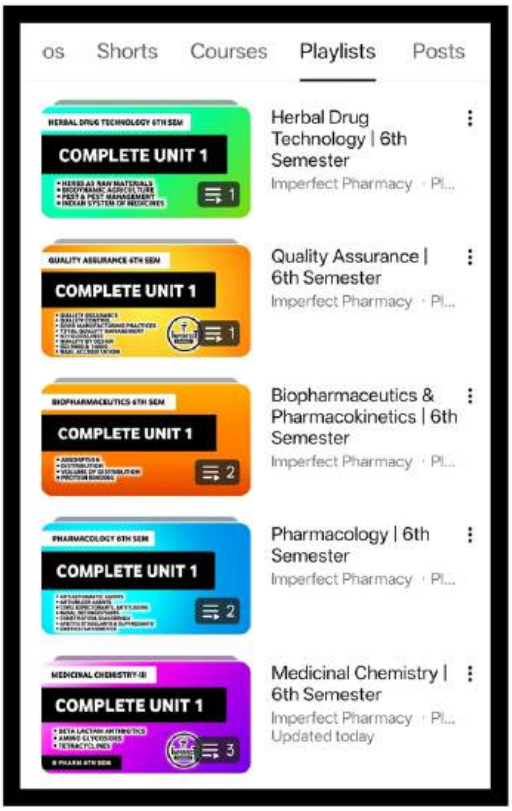

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② PHASE II REACTIONS

- Phase II Reactions are also known as Conjugation Reactions
- These reactions attach polar groups (e.g. glucuronic acid, sulfate, acetyl, methyl) to the drug making it highly water soluble.
- These reactions include :

ⓐ Glucuronide Conjugation
ⓑ Acetylation
ⓒ Methylation
ⓓ Sulfate Conjugation
ⓔ Glycine Conjugation
ⓕ Glutathione Conjugation

ⓐ Glucuronide Conjugation

- It is the process of addition of Glucuronic Acid.
- It is mediated by UDP-glucuronosyl transferases (UGTs)
- Examples: Chloramphenicol, aspirin, paracetamol etc.

ⓑ Acetylation

- It is the process of addition of Acetyl Group.
- It is mediated by N-Acetyltransferases.
- Example: Sulfonamides, isoniazid.

ⓒ Methylation

- It is the process of addition of Methyl Group.
- It is mediated by Methyltransferases.
- Example: Methyldopa, Mercaptopurine.

ⓓ Sulfate Conjugation

- It is the process of addition of Sulfate Group.
- It is mediated by Sulfotransferases.
- Example: Chloramphenicol, Methyldopa etc.

ⓔ Glycine Conjugation

- It is process of addition of Glycine to the drugs.
- It is mediated by Glycine-N-Acetyltransferases.
- Example: Salicylates, Nicotinic Acid etc.

ⓕ Glutathione Conjugation

- It is the process of addition of Glutathione.
- It is mediated by Glutathione-S-Transferases.
- Example: Paracetamol

FACTORS AFFECTING DRUG METABOLISM

There are various factors affecting drug metabolism as follows:

- Age
- Genetics
- Liver Health
- Gender
- Diet and Lifestyle
- Drug Interactions

① AGE

- Newborn babies shows slow metabolism as their liver is not fully developed.
- Liver functions decline with age, hence eldely people also shows slow metabolism.

② Genetics

- Some people naturally break down drugs faster or slower due to differences in their genes.

③ Liver Health

- If the liver is damaged (due to any liver disease), it cannot process drugs properly.

④ Gender

- Some drugs speed up or slow down metabolism when take together.

⑤ Diet and Lifestyle

- Grapefruit Juice slows metabolism of some drugs, leading to higher drug levels.
- Smoking & Alcohol increase metabolism, making some drugs work less effectively.

⑥ Gender

- Men and women process some drugs differently due to hormones.

EXCRETION

- Excretion is the process by which a drug and its metabolites are removed from the body primarily through urine, bile/ feces or other biological fluids.
- It is the final step in the process of drug elimination from the body.

IMPORTANCE OF EXCRETION

- Excretion is essential for:
  - Terminating drug action once its therapeutic purpose is fullfilled.
  - Preventing drug accumulation, which can lead to toxicity.
  - Help determining dosing interval & drug choice in patient with organ dysfunction.

ROUTES OF DRUG EXCRETION

There are two major routes of drug excretion:

① Renal excretion
② Non-renal excretion

Renal Excretion Of Drugs

Renal excretion is the process by which drugs & their metabolites are eliminated from the body through the kidney via urine.

Steps In Renal Excretion

Renal excretion involves 3 main steps:

1. Glomerular filtration
2. Tubular secretion
3. Tubular reabsorption

① GLOMRULAR FILTRATION

- Occurs in glomerulus.
- Only (free) unbound drug in plasma is filtered.
- Filtration rate depends on:
  - Renal blood flow
  - Glomerular filtration rate (GFR)
  - Drug size and binding.

② TUBULAR SECRETION

- Happens in the proximal tubule.
- Active process using transporters.
- Two types:
  - Organic ~~Aio~~ Anion Transporters (OAT) - for acidic drug (eg penicillin)
  - Organic Cation Transporters (OCT) - for basic drugs (e.g. morphine)
- Not affected by protein binding.

③ TUBULAR REABSORPTION

- Passive process, mostly in distal tubule.
- Depends on:
  - Lipid solubility of the drug
  - Urine pH
  - Drug ionization (non-ionized = more reabsorbed)
- Weak acids are reabsorbed more in acidic urine; weak bases in alkaline urine.

Factors Affecting Renal Excretion Of Drugs

- Renal excretion involves three major processes : Glomerular filtration, tubular secretion and tubular reabsorption.
- Several physiological, pharmacological and pathological factors influence how efficiently drugs are excreted by the kidneys.

① Plasma Protien Binding

- Only free (unbound) drugs in plasma can undergo glomerular filtration.
- Highly protein bound drugs (e.g. warfarin, diazepam) have reduced filtration.
- However, protein binding does not prevent active tubular secretion, as the drug associates from protein to maintain equillibrium.

② Renal Blood Flow

- Increased renal blood flow increases glomerular filtration & delivery of drug to the kidneys.
- Reduced renal perfusion (e.g heart failure, shock, dehydration) decreases excretion.

③ Glomerular Filtration Rate (GFR)

- Drugs are filtered at the glomerular if not protein-bound.
- GFR determines the volume of plasma filtered per unit time (normal ~ 120 mL/min)
- Decreased GFR (e.g., in kidney disease, aging) reduce drug clearance and may lead to accumulation and toxicity.

④ Active Tubular Secretion

- In the proximal tubule, drugs are secreted into the tubular lumen via specific transporters :

- Organic Anion Transporters (OAT) for weak acids (eg penicillin).
- Organic Cation Transporters (OCT) for weak bases (e.g morphine).

- This process is saturable and subject to competetion:
- E.g. probenecid inhibits secretion of penicillin, increasing its plasma level.

- Aging and renal impairment reduce active secretion capacity.

⑤ Tubular Reabsorption

- In the distal tubule, drugs may be reabsorbed back into the bloodstream by passive diffusion.
- Depends on :
  - Lipid solubility - Lipophilic drugs are reabsorbed more.
  - Ionization - Non-ionized drugs cross membranes easily.
  - Urine pH - Determines drug ionization state.
- Weak acids are reabsorbed in acidic urine (e.g aspirin).
- Weak bases are reabsorbed in alkaline urine (e.g. amphetamine).
- Reabsorption reduces renal excretion and prolongs drug action.

⑥ URINE pH

- Affects ionization of week acids and bases, thereby influencing reabsorption.
- Manipulating urine pH can enhance a drug elimination in overdose:
- Alkanization (e.g, with sodium bicarbonate) promote excretion of weak acids.
- Acidification (e.g., with ammonium chloride) promotes excretion of weak bases.

⑦ AGE

- Neonates have immature kidneys → low GFR, tubular secretion, and reabsorption.
- Drug elimination is slower; dosing must be adjusted to avoid accumulation.
- Elderly indivisuals often have reduced renal function even if creatine is normal.
- Renal clearance decreases → longer half-life and risk of toxicity.

⑧ DISEASE STATES

- Renal diseases (e.g. glomerulonephritis, chronic kidney disease) reduce GFR and secretion.
- Cardiovascular conditions (e.g. heart failure) reduce renal perfusion and thus excretion.
- Hepatic diseases can impair metabolism, altering the quantity of drug available for excretion.

⑨ Drug Interactions

- Co-administered drugs may compete for the same transporters, altering excretion :
- Example : Probenecid inhibits OAT, reducing renal clearance of penicillin.
- Some drugs can inhibit renal transporters and increase toxicity of co-administered drugs (e.g., cimetidine reduces secretion of creatinine).

⑩ Physiochemical Properties Of Drug

- Molecular size : Small molecules are filtered more easily.
- Lipid solubility : Lipophilic drugs are more likely to be reabsorbed.
- Ionization : Ionized (charged) drugs are less reabsorbed and more excreted in urine.

Non Renal Routes For Drug Excretion

- Non-renal excretion refers to the elimination of drugs and their metabolites from the body via routes other than kidneys.
- These include billiary, pulmonary, salivary, sweat, lacrimal, mammary, and skin/ gastrointestinal (GI) mucosa excretion.

① Billiary Excretion

- Drugs are secreted into bile by liver transporters like P-gp, MRP, BCRP.
- Molecular weight > 300 Da and conjugated (glucoronide) compounds are preferred.
- Excreted into bile → Intestine → Feces.
- Some drugs undergo enterohepatic circulation and get reabsorbed, prolonging half-life.

Examples: Rifampin, Erythromycin, Estrogen, Digoxin.

② Pulmonary Excretion

- Volatile substances and gases are excreted via lungs through passive diffusion.
- Depends on drug's vapour pressure, lipid solubility and respiratory rate.
- Rapid excretion allows fat recovery after inhaled anesthesia.

Examples: Halothen, Isoflurane, nitrous oxide, Alcohol.

③ Salivary Excretion

- Drugs enter saliva by passive diffusion or active transport.
- Salivary excretion may cause unpleasant taste or local irritation.
- Swallowed drug can be reabsorbed (entero - salivary cycling).
- Examples - Lithium, Phenytoin, Rifampin, Iodide.

④ Sweat And Sebaceous Glands

- Small, lipophilic drugs diffuse into sweat.
- Usually insignificant for drug elimination.
- Can cause skin irritation or affect body odor.
- Examples : Rifampin, Heavy metals (e.g. arsenic, lead), some antibiotics (traces).

⑤ Breast Milk

- Drugs passively difuse into breast milk (slightly acidic → favors basic drugs).
- Lipid - soluble, low molecular weight, and less protein - bound drugs transfer easily.
- May cause adverse effects in infants due to immature liver/ kidney function.
- Examples : Tetracyclines, Chloramphenicol, Lithium, opioids.

⑥ GIASTROINTESTINAL (GI) TRACT

- Drugs may be directly secreted into intestinal lumen or excreted unchanged via feces.
- Also included unabsorbed oral drugs.
- Especially relevant for oral drugs with poor absorption or billiary excretion.
- Examples : Vancomycin (oral), neomycin, tetracyclines.

BIOAVAILABILITY

- We know Bioavailability as fraction of administered drug that reaches the systemic circulation in unchanged form.
- In Biopharmaceutics is discovered in terms of how dosage form & route of administration affect how much drug reaches systemic circulation.
- So here we can define Bioavailability as "Rate & extent to which the above active ingredient (drug) is absorbed from a drug product & becomes available at site of action or in systemic circulation.

KEY ASPECTS

- It measures drug absorption & first pass metabolism.
- It is expressed in percentage.
- By IV Route, Bioavailability is almost 100%.
- For oral or other routes, bioavailability can be reduced by incomplete absorption, enzymatic degradation or first pass metabolism.

Objectives Of Bioavailability

- To assess how quickly and how much of the drug is absorbed into the bloodstream.
- To compare different formulations or routes of administration (e.g. tablet vs injection).
- To help in the development and optimization of effective dosage forms.
- To evaluate the impact of food, other drugs or physiological conditions on drug absorption.
- To generate data needed for regulatory approval of new or generic drugs.
- To ensure consistent therapeutic effects and minimize side effects.
- To study the extent of first pass metabolism in orally administered drugs.

Absolute Bioavailability

- Absolute bioavailability is the measure of the extent to which a drug reaches the systemic circulation when given by a non-intravenous route (like oral or intramuscular), compared to an intravenous (IV) dose of the same drug.
- IV administration is used as the reference standard, because it delivers 100% of drug directly into the bloodstream – no absorption barrier.

Significance :

- Helps determine how effective an oral or other non-IV dosage forms is compared to IV.
- Important during drug (new drug) development and clinical trial phases.

Formula :

$$Fa = \left(\frac{AUC_{oral}}{AUC_{IV}}\right) \times \left(\frac{Dose_{IV}}{Dose_{oral}}\right) \times 100$$

Where :

- AUC = Area under the curve (plasma drug concentration vs time)
- AUC reflects how much drug is present in systemic circulation over time.

Example:

A drug is given orally (100 mg) and IV (50 mg)
AUC from oral = 200 µg·h/mL
AUC from IV = 400 µg·h/mL

$$Fa = \left(\frac{200}{400}\right) \times \left(\frac{50}{100}\right) \times 100 = 25\%$$

Interpretation: Only 25% of the oral doses reaches the systemic circulation — rest is lost due to incomplete absorption or first-pass metabolism.

Relative Bioavailability

- Relative bioavailability compares the bioavailability of a drug from one formulation or route of administration to another non-IV formulation or route of administration (reference) of the same drug.
- The reference is typically an established standard formulation (e.g. an oral solution, a different tablet formulation, or a different non-IV route).
- This is often used when an IV formulation is not available or feasible for comparison.

Significance :

- Used in bioequivalence studies to compare a test formulation (e.g. generic) to a reference (e.g., innovator drug).
- Required for regulatory approval of generics.

Formula :

$$F_R = \left(\frac{AUC_{test}}{AUC_{reference}}\right) \times \left(\frac{Dose_{reference}}{Dose_{test}}\right) \times 100$$

Example :

- Test (generic) drug : 100 mg , AUC = 220 μg·h/mL
- Reference (brand) drug : 100 mg , AUC = 200 μg·h/mL

$$F_R = \left(\frac{220}{200}\right) \times \left(\frac{100}{100}\right) \times 100 = 110\ \%$$

Interpretation : The best formulation has 110 % relative bioavailability compared to the reference — it delivers slightly more drug to the bloodstream.

Measurement Of Bioavailability

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

1. Pharmacokinetic methods
2. Pharmacodynamic methods

Pharmacokinetic Methods

- Pharmacokinetic methods commonly used to quantify bioavailability using measurable biological samples (mostly blood or urine).
- It can be further subdevided into two types :

a. Plasma Drug Concentration Method
b. Urinary Drug Excretion Studies

a. Plasma Drug Concentration Method

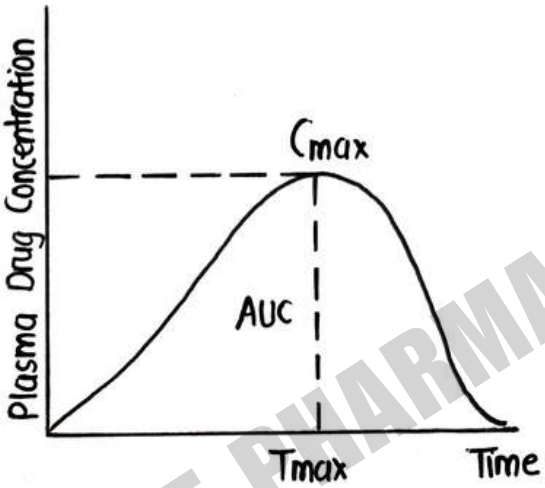
This is the most reliable and widely used method to measure bioavailability.

Principle

- When a drug is absorbed into the systemic circulation, it appears in the plasma.
- Measuring drug concentration in plasma over time helps determine both rate and extent of absorption.

Procedure

- The drug is administered (oral, IV route).
- Blood samples are collected at various time intervals.
- Plasma is separated and analyzed for drug concentration.
- A plasma concentration vs time graph is plotted.



KEY PHARMACOKINETIC PARAMETERS

ⓐ Cmax -
- It is minimum Plasma Drug Concentration.
- Indicates rate of absorption.
- Higher Cmax = Faster absorption.

ⓑ Tmax -
- Time to reach Cmax
- Indicates how quickly drug is absorbed.

ⓒ AUC -
- It is Area Under Curve
- Reflects the total exposure of drug in plasma.
- Directly proportional to the extent of absorption.

Uses

- To compare two different formulations (test vs reference).
- To study bioequivalance.
- To optimize dosage form designe.

ⓑ Urinary Drug Excretion Studies

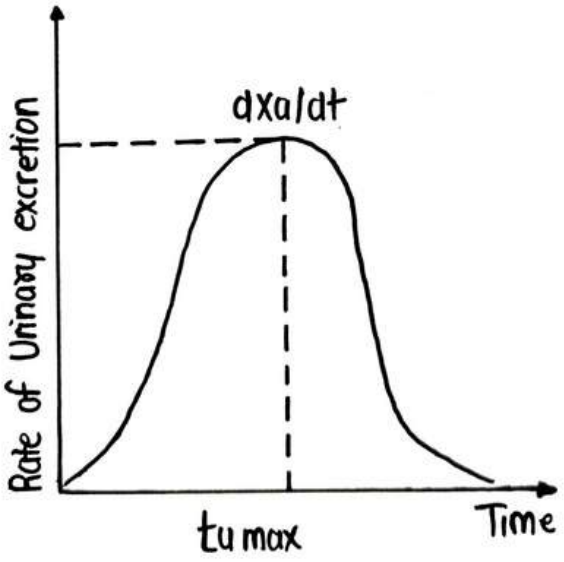
This method is based on measuring the amount of unchanged drug excreted in the urine over time.

Principle

- Only the absorbed drug can enter the bloodstream and be filtered by the kidneys.
- Therefore, the amount of unchanged drug excreted in urine reflects the extent of drug absorption.

Procedure

- Administer the drug.
- Collect urine samples at regular intervals (e.g. every 2 hours).
- Analyze each sample for unchanged drug content.
- Plot : Rate of urinary excretion (dDu/dt) vs MidPoint Time (T).



Key Parameters

- dXu/dt : - It is the maximum urinary excretion rate.
  - Gives an idea about rate of absorption.

- Tu max : - Time of maximum urinary excretion rate.
  - Similiar to Tmax in plasma studies.

- Xu : - Total amount of Drug Excreted in Urine
  - Similiar to AUC of Plasma Drug concentration studies

Conditions For Use

- The drug must be : - Excreted unchanged in urine.
  - Excreted is sufficient quantity for accurate measurement.

- Advantages : - Non-invasive compared to blood sampling.
  - Useful when plasma concentration measurement is difficult.

- Limitations : Cannot be used for drugs that :
  - Are extensively metabolized.
  - Are not excreted via urine.
  - Have very low renal excretion.

PHARMACODYNAMIC METHOD

- When direct plasma or urine measurements are not possible, bioavailability can be assessed using the pharmacological effects (i.e. body's response to the drug).
- This method is useful when :
  - Drug concentration measurement is tough.
  - Drug acts locally (e.g. eye drops, skin creams)
  - No reliable analytical method is available.
- It has two main types :

① Acute pharmacological response
② Therapeutic response.

① ACUTE PHARMACOLOGICAL RESPONSE METHOD

Principle

Bioavailability is estimated by measuring the immediate pharmacological effect of the drug, which correlates with its concentration at the site of action.

Examples

- Change in blood pressure after an antihypertensive drug.
- Pupil dilation after eye drops like atropine.
- Muscle contraction / inhibition in lab animals.

Limitations

- Response may not always directly correlate with concentration.
- Subjective variation in measurement.
- Tolerance or desensitization can affect results.

② THERAPEUTIC RESPONSE METHOD

Principle

Bioavailability is evaluated by comparing the clinical outcome or therapeutic effect of the drug.

Examples

- Pain relief with analgesics (e.g. paracetamol).
- Seizures control with antiepileptic drugs.
- Blood glucose reduction in diabetic patients after antidiabetic treatment.

In Vitro Drug Dissolution Methods

- In vitro drug dissolution testing models are laboratory methods used to measure how quickly and how much of a drug dissolves from its dosage form (like a tablet or capsule) into a liquid, outside the body (i.e., in vitro).
- These tests simulate conditions in the human gastrointestinal (GI) tract and are important for predicting how the drug will behave in the body (in vivo).

Purpose

- To ensure consistent drug release from batch to batch.
- To predict bioavailability and bioequivalence.
- To support formulation development and quality control.

Main types of In Vitro Dissolution Methods

- Usp Apparatus I (Basket Method)
- USP Apparatus II (Paddle Method)
- USP Apparatus III (Resiprocrating Cylinder)
- USP Apparatus IV (Flow - through cell)
- USP Apparatus V - VII

① USP APPARATUS I (BASKET METHOD)

- The tablet / capsule is placed inside a rotating basket submerged in a dissolution medium.
- Suitable for capsule and floating dosage forms.

② USP APPARATUS II (PADDLE METHOD)

- A paddle stirs the dissolution medium while the dosage forms rests the at bottom.
- Commonly used for tablets.

③ USP APPARATUS III (RECIPROCATING METHOD)

- Used for controlled - release formulations.
- The drug moves up and down between different compartments simulating GI conditions.

④ USP APPARATUS IV (FLOW - THROUGH CELL)

- Medium flows through a cell containing the dosage form.
- Suitable for poorly soluble drugs or modified - release forms.

⑤ USP APPARATUS V-VII

- Less common, used for special dosage forms like transdermal patches or chewables.

Key Parameters Measured

- % drug released vs Time
- Dissolution rate
- T90 (time to release 90% of drug)

Why It's Important

- It's a predictive tool for in Vivo performance.
- Saves time and cost before clinical trials.
- Required by regulatory authorities for approval of generic drugs.

In Vitro - In Vivo Correlation (IVIVC)

- In Vitro - In Vivo Correlation (IVIVC) is predictive mathematical model that describes the relationship between a drug's in vitro dissolution or release and its in vivo absorption (usually measured as plasma drug concentration or exposure).

Why IVIVC is Important

- It helps in predicting how a drug will behave in the human body using laboratory (in vitro) test.
- It can reduce the need for expensive and time-consuming clinical studies.
- Supports formulation development, bioequivalence testing, and regulatory approval, especially for modified-release formulations.

Key Concepts

① **In Vitro Data:** Usually comes from dissolution testing (e.g. % drug dissolved over time).

② **In Vivo Data:** Comes from pharmacokinetic studies (e.g., plasma concentration vs time curves).

③ **Correlation:** A mathematical link that allows prediction of in vivo behaviour from in vitro results.

Levels Of IVIVC (According To FDA)

① Level A (Point -to- Point Correlation):

- Strongest and most prefferred type.
- There is a direct relationship between in vitro dissolution time points and in vivo absorption time points.
- Example - 30 % dissolved = 30 % Absorbed.
- Allows full prediction of plasma drug concentration - time profiles.

② Level B (Stastiscal Moment Analysis):

- Compares mean in vitro dissolution time to mean residence/absorption time in vivo.
- Uses statistical moments, not point-to-point correlation.
- Less informative than Level A.

③ Level C (Single Point Correlation):

- Correlates one dissolution point (e.g., 60 min) with one pharmacokinetic parameter (eg. Cmax or AUC).
- Simple but limited predictive value.

④ Multiple Level C:

- Improves on Level C by using multiple in vitro time points and correlating them with multiple PK parameters.
- Still not as powerful as Level A but better than single point.

EXAMPLE

- Suppose a sustained - release tablet releases 50 % of its drug in 2 hours (in vitro) and in a pharmacokinetic study, the same amount of drug is absorbed in 2 hours (in vivo).
- If this pattern holds across other time points, a level A IVIVC exits.

CONCLUSION

- IVIVC is a powerful tool in pharmaceutical development that connects lab results with real - world drug behaviour.
- A strong IVIVC helps save time, reduce costs, and supports faster regulatory approval.

BIOEQUIVALANCE STUDIES

- Bioequivalance means that two medicines (usually a brand-name drug and its generic version) work same in the body.
- They release the same amount of active drug at same speed and have the same effect.
- Bioequivalance refers to the similiarity between two drug products in terms of:
  - Rate of absorption (how fast the drug gets into bloodstream).
  - Extent of absorption (how much of drug gets into bloodstream).

- When two drugs products are equivalent, it means -
  - They have comperable bioavailability (i.e. they reach similiar drug levels in the blood).
  - They produce similiar therapeutic effects and safety profiles.
  - They are usually tested in healthy volunteers using pharmacokinetic studies, which compare parameters like:
    * Cmax (maximum concentration of drug in the blood)
    * Tmax (Time to reach Cmax)
    * AUC (Area under the curve, which shows total drugs exposure)

- Regulatory agencies like the FDA or EMA accept two drugs ~~or~~ as bioequivalent if their Cmax and AUC values fall within 80% to 125% of each other.

Example

If you take a 500 mg tablet of Brand A and a 500 mg tablet of Generic, B and both:

- Reach the same peak level in your blood.
- Take the same time to reach that level.
- Stay in your system for the same time.

The Brand A and B (Generic) are considered bioequivalent.

Need Of Bioequivalent Studies

These studies are essential for regulatory approval of generic drugs, ensuring they are just as safe and effective as the original product.

BCS Classification Of Drugs

- The term BCS stands for Biopharmaceutical classification system,
- It is a scientific framework for classifying drugs based on their solubility & permeability.
- It helps in predicting the drug absorption & bioavailability, and it is widely used in drug development and regulation.

Class	Solubility	Permeability	Absorption	Example
I	High	High	Good	Metaprolol
II	Low	High	Variable	Nifedipine
III	High	Low	Variable	Cimetidine
IV	Low	Low	Poor	Furosemide

Class I

- Drug in this class are highly soluble in nature & can easily permeate intestinal membrane.
- They rapidly absorbed after oral administration.
- Exhibit good bioavailability.
- Drugs in this category are often considered ideal for oral delivery.
- Examples : Metaprolol, Propanolol.

CLASS II

- These drugs have poor solubility but can easily permeate the intestinal membrane.
- The bioavailability of these drugs can be improved by formulations that enhance solubility.
- These drugs are also suitable for controlled release developments.
- Examples : Ketaconazole, Ibuprofen, Phenytoin.

CLASS III

- Drug in these class have good solubility but having difficulty in permeating intestinal membrane.
- Changes in the integrity of gastrointestinal membrane, such as from disease or drug interactions, may affect bioavailability.
- Presence of food can alter absorption process.
- Example : Cimetidine, Atenolol, Acyclovir.

CLASS IV

- Drugs in these class have poor solubility & permeability.
- They have poor absorption & bioavailability.
- These drugs may require novel drug delivery system.
- Drug development in this categogary is a challenging process.
- Example : Furosemide.

METHODS FOR ENHANCEMENT OF BIOAVAILABILITY

- Enhancing the dissolution rate and bioavailability of poorly soluble drugs is a critical challenge in pharmaceutical development.
- Poorly solubility can limit drug absorption in the gastrointestinal tract, leading to subtherapeutic effects.
- Several formulation and technological approaches are used to improve these properties :

① Particle Size Reduction (Micronization / Nanonization)

Principle : Reducing particle size increases the surface area available for dissolution.

Techniques :
- Micronization using jet mills or ball mills.
- Nanonization using high-pressure homogenization or wet milling.

Advantage : Simple, effective for BCS Class II drugs.

Limitation : May lead to aggregation, poor flow properties.

② Solid Dispersions

Principle : Dispensering the drug in a water-soluble carrier improves wettability and reduces crystallinity.

Types :
- Eutectic Mixtures
- Solid solutions
- Glass solutions or Amorphous solutions.

Carriers : PEG, PVP, HPMC etc.

Advantages : Increase solubility, dissolution rate.

Challenges : Stability and scalability.

③ Use of Surfactants

Principle: Surfactants reduce surface tension and improve wetting and solubilization.

Examples: Sodium Lauryl Sulphate (SLS), Poloxamers, Tween 80.

Advantages: Enhanced dissolution and bioavailability.

Consideration: Surfactant concentration must be optimized to avoid GI irritation.

④ Salt Formation

Principle: Converting a poorly soluble drug into a salt form can improve solubility.

Criteria: Drug must have ionizable functional groups.

Examples: Aspirin (Acetylsalicyclic acid) into its sodium salt.

Limitations: Not all drugs are suitable for salt formation, stability issues.

⑤ Solid Lipid Nanoparticles (SLNs) & Nanostructured Lipid Carriers (NLCs)

Principle: Drugs are incorporated into lipid matrices at the nanoscale.

Benefits: Controlled release, enhanced bioavalability, biocampatibility.

Applications: Suitable for lipophilic drugs.

⑥ Complexation

Cyclodextrin Complexes :
- Cyclodextrins (e.g. β-cylodextrin) form inclusion complexes with hydrophobic drugs.
- Improve solubility, stability and taste.

Ion Exchange Resins :
- Used for taste masking and controlled release.

⑦ pH Modification

Principle : Using buffers or adjusting pH locally to increase solubility.

Examples : Adding Citric acid or sodium biocarbonate to modify microenvironment pH.

Application : Often used in oral suspensions or fast-dissolving tablets.

⑧ Amorphous Formulation

Amorphous Drugs have higher solubility than their crystalline counterparts.

Techniques : Spray drying, Melt quenching.

Challenge : Stability issues due to tendency to recrystallize.

THANK YOU

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