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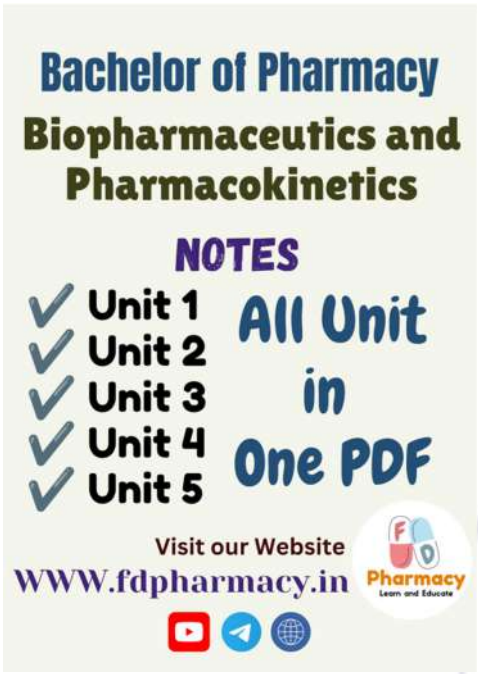
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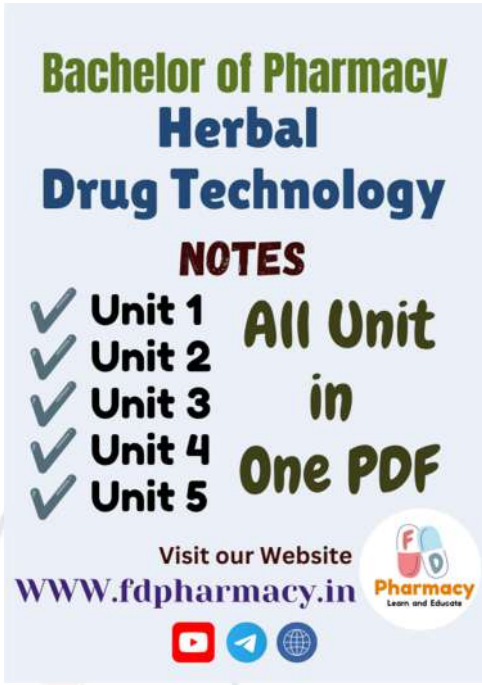
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BIOPHARMACEUTICS AND PHARMACOKINETICS

UNIT 2

TOPIC :

- **Elimination :** Drug metabolism and basic understanding metabolic pathways renal excretion of drugs, factors affecting renal excretion of drugs, renal clearance, Non renal routes of drug excretion of drugs

Elimination of Drugs

Drug elimination is the process by which a drug is removed from the body after administration. It is an important part of pharmacokinetics.
Elimination mainly occurs through:

1. **Drug Metabolism (Biotransformation)** – conversion of drugs into metabolites.
2. **Drug Excretion** – removal of drugs and metabolites from the body.

The organs mainly involved are:

- Liver
- Kidneys
- Lungs
- Skin
- Intestine

Metabolism (Biotransformation)

Metabolism is also known as Biotransformation**.**
It is the process by which the body converts a drug into simpler, more water-soluble and easily excretable forms.
The main purpose of metabolism is:

- To detoxify drugs
- To convert lipid soluble drugs into water soluble forms
- To help elimination through urine or bile

The primary site of drug metabolism is the **liver**.
Other sites include:

- Kidneys
- Intestine
- Lungs
- Plasma

Most metabolic reactions occur through enzymes present in the liver.

Importance of Drug Metabolism

Drug metabolism is important because it:

- Determines duration of drug action
- Controls intensity of drug effect
- Helps removal of drugs from body
- Prevents drug accumulation and toxicity

Conversion During Metabolism

Drug metabolism may convert:

Drug Form	Converted Into
Active Drug	Active Metabolite
Active Drug	Inactive Metabolite
Inactive Drug (Prodrug)	Active Metabolite

Examples

- Codeine → Morphine (active metabolite)
- Diazepam → Oxazepam
- Enalapril → Enalaprilat

Types of Metabolic Reactions

There are mainly two phases of metabolism:

1. Phase I Reactions

These reactions introduce or expose functional groups in the drug molecule.

Main reactions:

- Oxidation
- Reduction
- Hydrolysis
- Cyclization
- Decyclization

Phase I reactions usually make drugs:

- Slightly more water soluble
- More chemically reactive

These reactions involve:

- Microsomal enzymes
- Non-microsomal enzymes

PHASE I REACTIONS

1. Oxidation

Oxidation is the process of:

- Addition of oxygen
  OR
- Removal of hydrogen from a drug molecule

These reactions are mainly carried out by:

- Cytochrome P450 enzymes (CYP450)

Importance

- Produces more polar metabolites
- Helps easy excretion

Examples

- Phenytoin
- Phenobarbitone
- Propranolol

Features

- Most common metabolic reaction
- Mainly occurs in liver microsomes

2. Reduction

Reduction is the process of:

- Addition of hydrogen
  OR
- Removal of oxygen

Reduction reactions are less common than oxidation.

Examples

- Chloramphenicol
- Warfarin

Characteristics

- Occurs in low oxygen conditions
- Mediated by reductase enzymes

3. Hydrolysis

Hydrolysis is the breakdown of a drug by addition of water.

It commonly occurs in:

- Esters
- Amides

Enzymes involved

- Esterases
- Amidases
- Peptidases

Examples

- Aspirin
- Procaine
- Lidocaine

Importance

- Splits large molecules into simpler forms

4. Cyclization

Cyclization is the conversion of a straight chain compound into a cyclic compound.

Example

- Proguanil → Cycloguanil

Importance

- May increase drug activity

5. Decyclization

Decyclization involves opening of a cyclic ring structure.

Example

- Barbiturates

Importance

- Produces metabolites suitable for excretion

2. Phase II Reactions (Conjugation Reactions)

These reactions attach polar groups to the drug molecule.
Examples of attached groups:

- Glucuronic acid, Sulfate
- Acetyl group, Methyl group
- Glycine
- Glutathione

Phase II reactions produce:

- Highly water soluble metabolites
- Easily excretable products

PHASE II REACTIONS (CONJUGATION)

Phase II reactions attach endogenous substances to drugs.
These reactions usually produce:

- Inactive metabolites
- Highly water soluble compounds

1. Glucuronide Conjugation

It is the addition of **Glucuronic Acid** to a drug molecule.

Enzyme

- UDP-Glucuronosyl Transferase (UGT)

Examples

- Chloramphenicol , Aspirin, Paracetamol

Importance

- Most common conjugation reaction
- Increases water solubility greatly

2. Acetylation

Acetylation is the addition of an acetyl group.

Enzyme

- N-Acetyl Transferase

Examples

- Sulfonamides, Isoniazid

Importance

- Genetic variation affects acetylation rate
- People may be slow or fast acetylators

3. Methylation

Methylation is the addition of a methyl group.

Enzyme

- Methyl Transferase

Examples

- Methyldopa
- Mercaptopurine

Importance

- Often decreases drug activity

4. Sulfate Conjugation

In this reaction, sulfate group is attached to the drug.

Examples

- Paracetamol
- Steroid hormones

Importance

- Enhances excretion through urine

5. Glycine Conjugation

Drug combines with glycine amino acid.

Example

- Salicylic acid

Importance

- Helps detoxification

6. Glutathione Conjugation

Drug combines with glutathione.

Importance

- Detoxifies toxic metabolites
- Protects liver cells

Example

- Detoxification of paracetamol toxic metabolite

Factors Affecting Drug Metabolism

→ Drug metabolism is influenced by many physiological, pathological and environmental factors. These factors can increase or decrease the rate of metabolism and thereby alter drug action, duration and toxicity.

1. Age

Age greatly affects drug metabolism.

In Neonates (Infants)

- Liver enzymes are not fully developed.
- Drug metabolism is slow.
- Drugs remain longer in the body.
- Risk of toxicity is high.

Example

- Chloramphenicol may cause "Gray Baby Syndrome".

In Elderly People

- Liver size and blood flow decrease.
- Enzyme activity reduces.
- Drug metabolism becomes slower.

Result

- Increased drug action
- Higher risk of adverse effects

2. Genetic Factors

Genetic makeup affects enzyme activity in different individuals.
Some people metabolize drugs:

- Rapidly
- Slowly

This is called **Pharmacogenetic variation**.

Examples

- Slow acetylators metabolize Isoniazid slowly.
- CYP450 enzyme variations alter metabolism of many drugs.

Effects

- Therapeutic failure
- Drug toxicity

3. Species Difference

Different animal species metabolize drugs at different rates.

Example

- Cats have poor glucuronide conjugation.
- Dogs metabolize some drugs faster than humans.

Importance

- Important in animal studies and toxicology.

4. Sex

Hormonal differences between males and females may affect metabolism.

Examples

- Some drugs are metabolized faster in males.
- Pregnancy alters liver enzyme activity.

Result

- Difference in drug response between genders.

5. Liver Disease

Liver is the major site of drug metabolism.

Diseases like:

- Hepatitis
- Cirrhosis
- Liver failure

reduce enzyme activity.

Effects

- Reduced metabolism
- Drug accumulation
- Increased toxicity

6. Cardiac Disease

Heart diseases reduce blood flow to the liver.

Result

- Less drug reaches liver
- Slower metabolism

Example

- Congestive heart failure

7. Nutrition and Diet

Diet influences enzyme activity.

Malnutrition

- Reduces enzyme synthesis
- Slows metabolism

High Protein Diet

- Increases enzyme activity

Certain Foods

Some foods inhibit metabolism.

Example

- Grapefruit juice inhibits CYP3A4 enzyme.

8. Enzyme Induction

Some drugs increase synthesis of metabolizing enzymes.
This increases rate of metabolism.

Examples

- Rifampicin
- Phenobarbitone
- Carbamazepine
- Phenytoin

Effects

- Reduced drug action
- Shorter duration of action
- Therapeutic failure

9. Route of Administration

The route by which a drug is given affects metabolism.

Oral Route

Drugs undergo **First Pass Metabolism** in liver.

Result

- Reduced bioavailability

Intravenous Route

- Bypasses first pass effect.

Excretion

Excretion is the process by which drugs and their metabolites are removed from the body through urine, bile, feces or other biological fluids.

It is the final step in drug elimination from the body.

The main purpose of excretion is to remove:

- Unchanged drugs
- Drug metabolites
- Toxic substances

Importance of Excretion

Drug excretion is essential because it:

- Terminates drug action after therapeutic effect is completed
- Prevents accumulation of drugs in the body
- Reduces risk of toxicity
- Maintains normal drug concentration in blood
- Helps determine proper dosage regimen
- Helps in selection of drugs in patients with kidney or liver dysfunction

Routes of Drug Excretion

There are two major routes of drug excretion:

1. Renal Excretion

(Excretion through kidneys)

2. Non-Renal Excretion

(Excretion through other routes)

1. RENAL EXCRETION

→ Renal excretion is the most important route of drug elimination.
→ The kidneys remove drugs mainly through urine.

Mechanism of Renal Excretion

Renal excretion occurs by three processes:

1. Glomerular Filtration
2. Tubular Secretion
3. Tubular Reabsorption

1. Glomerular Filtration

In this process:

- Free drug molecules pass from blood into glomerular filtrate.

Only:

- Low molecular weight
- Unbound drugs are filtered.

Protein-bound drugs are not filtered easily.

Characteristics

- Passive process
- Depends on blood flow to kidneys

2. Tubular Secretion

In this process:

- Drugs are actively secreted from blood into renal tubules.

This occurs mainly in:

- Proximal convoluted tubule

Features

- Active transport process
- Requires energy
- Can occur even for protein-bound drugs

Examples

- Penicillin
- Para-aminohippuric acid (PAH)

3. Tubular Reabsorption

In this process:

- Drugs move back from renal tubules into blood.

Lipid soluble and unionized drugs are reabsorbed easily.

Water soluble and ionized drugs are poorly reabsorbed and are excreted in urine.

Factors Affecting Reabsorption

- Urine pH
- Lipid solubility
- Degree of ionization

Factors Affecting Renal Excretion

1. Glomerular Filtration Rate (GFR)

- Reduced GFR decreases drug excretion.

2. Urine pH

- Acidic drugs are excreted faster in alkaline urine.
- Basic drugs are excreted faster in acidic urine.

3. Protein Binding

- Highly protein-bound drugs are excreted slowly.

4. Renal Blood Flow

- Reduced blood flow decreases excretion.

5. Age

- Infants and elderly have reduced renal function.

6. Disease Conditions

- Kidney diseases reduce drug excretion and increase toxicity.

Renal Clearance

The kidneys are the major organs responsible for elimination of drugs from the body.
Renal clearance helps to measure how efficiently the kidneys remove a drug from the blood.

It is an important pharmacokinetic parameter used in:

- Dose adjustment
- Determining kidney function
- Drug therapy monitoring

Definition

→ Renal clearance is the volume of plasma completely cleared of a drug by the kidneys per unit time.

Formula of Renal Clearance

$$Cl_R = \frac{Rate\ of\ urinary\ excretion}{Plasma\ drug\ concentration}$$

Where:

- Cl_R = Renal clearance
- Rate of urinary excretion = Amount of drug excreted in urine per unit time
- Plasma drug concentration = Drug concentration in blood plasma

NON-RENAL ROUTES OF DRUG EXCRETION

→ Non-renal excretion refers to the elimination of drugs and their metabolites through routes other than the kidneys.
→ These routes help remove drugs from the body when renal excretion is insufficient or when drugs possess special physicochemical properties.

Important Non-Renal Routes

Non-renal excretion includes:

1. Biliary Excretion
2. Pulmonary Excretion
3. Salivary Excretion
4. Sweat and Sebaceous Gland Excretion
5. Breast Milk Excretion
6. Gastrointestinal Excretion
7. Lacrimal (Tear) Excretion
8. Skin Excretion

1. Biliary Excretion

→ In biliary excretion, drugs are secreted from the liver into bile and then passed into the intestine.
→ Finally, drugs are removed through feces.

Mechanism

Drugs are transported into bile by hepatic transport proteins such as:

- P-glycoprotein (P-gp)
- MRP (Multidrug Resistance Proteins)
- BCRP (Breast Cancer Resistance Protein)

Characteristics

Drugs excreted through bile are usually:

- High molecular weight (>300 Da)
- Polar compounds

- Conjugated metabolites (especially glucuronides)

Process

- Liver → Bile → Intestine → Feces
- Enterohepatic Circulation
- Some drugs excreted in bile are reabsorbed from intestine back into blood.
- This process is called Enterohepatic Circulation.

Importance

- Prolongs drug half-life
- Increases duration of action

Examples

- Rifampicin
- Erythromycin
- Estrogens
- Digoxin

2. Pulmonary Excretion

The lungs excrete:

- Volatile substances
- Gases
- Vapors

This occurs mainly through passive diffusion across alveolar membranes.

Factors Affecting Pulmonary Excretion

- Vapour pressure of drug
- Lipid solubility
- Respiratory rate
- Pulmonary blood flow

Importance

Rapid pulmonary excretion helps recovery after inhalational anesthesia.

Examples

- Halothane
- Isoflurane
- Nitrous oxide
- Alcohol

3. Salivary Excretion

Some drugs enter saliva through:

- Passive diffusion
- Active transport

Usually only small amounts are excreted.

Characteristics

- Lipid soluble drugs diffuse easily
- Salivary pH affects drug diffusion

Effects

Salivary excretion may:

- Produce unpleasant taste
- Cause local irritation

Sometimes swallowed saliva may cause reabsorption of drug.
This is called Enterosalivary Cycling.

Examples

- Lithium, Phenytoin
- Rifampicin, Iodide

4. Sweat And Sebaceous Gland Excretion

→ Small amounts of drugs diffuse into sweat and sebaceous secretions.

Characteristics

Usually insignificant for total drug elimination.
Drugs excreted in sweat are mainly:

- Lipid soluble
- Non-ionized

Effects

May cause:

- Skin irritation
- Body odor
- Skin discoloration

Examples

- Rifampicin
- Heavy metals (e.g., arsenic)
- Trace amounts of antibiotics

5. Breast Milk Excretion

→ Some drugs pass from blood into breast milk by passive diffusion.

Characteristics

Drugs excreted in breast milk are usually:

- Lipid soluble
- Low molecular weight
- Less protein bound
- Weakly basic drugs

Since breast milk is slightly acidic, basic drugs concentrate more in milk.

Examples

- Morphine, Tetracycline, Chloramphenicol, Diazepam

6. Gastrointestinal (GI) Excretion

→ Some drugs are secreted directly into gastrointestinal tract.

→ These drugs are eliminated through feces.

Examples

- Heavy metals, Morphine

7. Lacrimal (Tear) Excretion

→ Small quantities of drugs may appear in tears.

Effects

- Eye irritation
- Discoloration of contact lenses

Example

- Rifampicin

8. Skin Excretion

→ Certain drugs may be excreted through skin cells and sebaceous glands.

→ Usually minor in amount.

Factors Affecting Non-Renal Excretion

- Lipid solubility
- Molecular weight
- Degree of ionization
- Protein binding
- Blood flow to excretory organs