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MEDICINAL CHEMISTRY - I

UNIT 1

TOPIC :

- **Drug metabolism**

Drug metabolism principles- Phase I and Phase II.

Factors affecting drug metabolism including stereo chemical aspects.



Drug Metabolism

- Drug metabolism (biotransformation) refers to the biochemical modification of drugs in the body, mainly by enzymes.
- Occurs primarily in the liver, but also in kidneys, lungs, intestines, and plasma.
- Purpose: Convert lipophilic drugs → hydrophilic metabolites to facilitate elimination.
- Outcomes of metabolism:
 - Drug inactivation (most common).
 - Activation of prodrugs (e.g., enalapril → enalaprilat).
 - Formation of toxic metabolites (e.g., paracetamol → NAPQI).

Principles of Drug Metabolism

1. Makes drugs more polar and water-soluble for renal or biliary excretion.
2. Occurs in two phases:
 - Phase I (functionalization) → introduces/exposes functional groups.
 - Phase II (conjugation) → adds polar endogenous groups.
3. Involves specific enzymes:
 - Phase I → Cytochrome P450 system, esterases, amidases.
 - Phase II → transferases (e.g., glucuronyl transferase, sulfotransferase).
4. May produce inactive, active, or toxic metabolites.

Phases of Drug Metabolism

Phase I Reactions (Functionalization)

- **Reactions:** Oxidation, reduction, hydrolysis, deamination.
- **Purpose:** Introduce or expose polar functional groups like -OH, -NH₂, -SH, -COOH.
- **Examples:**

- Oxidation of paracetamol → aminophenol.
- Reduction of nitrobenzene → aniline.
- Hydrolysis of aspirin → salicylic acid + acetic acid.
- **Stereochemistry:**
 - Enzyme systems often act stereoselectively.
 - Example: S-warfarin is metabolized faster and is more potent than R-warfarin.

Phase II Reactions (Conjugation)

- **Reactions:** Conjugation with endogenous molecules such as glucuronic acid, sulfate, acetate, glycine, glutathione, or methyl groups.
- **Purpose:** Further increase polarity → metabolites become highly water-soluble, inactive, and easily excreted.
- **Examples:**
 - Morphine → morphine-6-glucuronide (glucuronidation).
 - Salicylic acid → salicyluric acid (glycine conjugation).
 - Paracetamol → paracetamol sulfate (sulfation).
- **Stereochemistry:** Less stereoselective than Phase I, but minor differences exist.

Factors Affecting Drug Metabolism

1. Genetic factors

- Polymorphisms in metabolizing enzymes → variable responses.
- Example: *Slow acetylators* of isoniazid show higher toxicity.

2. Age

- Infants: Enzyme systems immature → slower metabolism (e.g., chloramphenicol → “gray baby syndrome”).
- Elderly: Decline in liver function → slower metabolism.

3. Physiological factors

- Sex differences, pregnancy, hormonal changes, nutritional status.

4. Liver function

- Hepatic diseases (cirrhosis, hepatitis, cancer) impair metabolism → drug accumulation and toxicity.

5. Diet and environmental factors

- Grapefruit juice → inhibits CYP3A4.
- Smoking, alcohol, and pollutants → induce liver enzymes.

6. Drug interactions

- Enzyme induction: Phenobarbital, rifampicin (increase metabolism → reduce drug effect).
- Enzyme inhibition: Cimetidine, ketoconazole (decrease metabolism → increase drug toxicity).

7. Stereochemical aspects

- Enantiomers may be metabolized differently due to enzyme stereospecificity.
- **Example:**
 - **Ibuprofen:** S-isomer is active; some R-isomer is converted to S-form.
 - **Thalidomide:** R-enantiomer is sedative, S-enantiomer is teratogenic.

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