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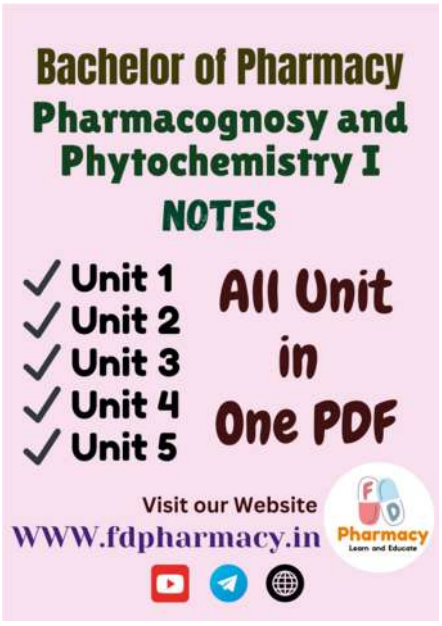
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MEDICINAL CHEMISTRY – I

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, –NH_2, –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 excretable.
- **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.