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MEDICINAL CHEMISTRY – I

UNIT 1

TOPIC :

- **Introduction to Medicinal Chemistry**

  History and development of medicinal chemistry

  Physicochemical properties in relation to biological action

  Ionization, Solubility, Partition Coefficient, Hydrogen bonding, Protein

  binding, Chelation, Bioisosterism, Optical and Geometrical isomerism.

Introduction to Medicinal Chemistry

- Medicinal chemistry is the science concerned with the discovery, design, synthesis, and development of new chemical compounds that can be used as therapeutic agents.
- It involves the study of existing drugs, their pharmacological actions, mechanisms, side effects, toxicities, and efforts to improve their activity through chemical modifications.
- It is an interdisciplinary research area, integrating knowledge from:
    - Organic chemistry (drug design, synthesis, chemical modifications)
    - Pharmacology (biological effects, mechanism of action)
    - Biochemistry & Molecular biology (drug-receptor interactions, enzyme inhibition)
    - Pharmaceutics (drug formulation, dosage forms)

Alternate definitions

1. Medicinal chemistry deals with the discovery and design of new therapeutic chemicals and their development into useful drugs.
2. It is the intersection of organic chemistry, pharmacology, and biology, aiming to discover and optimize drugs.
3. It combines expertise from chemistry and biology to study drug action, drug design, and quantitative structure–activity relationships (QSARs).

Scope of Medicinal Chemistry

- **Drug discovery and design** (rational drug design, computer-aided drug design).
- **Structure–Activity Relationship (SAR)** studies.
- **Quantitative Structure–Activity Relationship (QSAR)** for predicting biological activity.
- **Drug synthesis and development** for large-scale production.
- **Study of pharmacokinetics** (ADME – Absorption, Distribution, Metabolism, Excretion).
- **Study of pharmacodynamics** (mechanism of drug action).
- **Toxicology studies** (to ensure safety).
- **Optimization of drug formulations** for therapeutic use.

History and Development of Medicinal Chemistry

Ancient Period

- Use of plants, minerals, and animal products as medicine dates back to prehistoric times.
- Ancient Indian texts (Ayurveda) and Chinese medicine recorded herbal remedies.
- Ancient Greeks and Romans contributed significantly:
    - Hippocrates (460–377 BC) – Father of Medicine, described therapeutic uses of plants.
    - Dioscorides – Compiled *De Materia Medica*, a medicinal plant guide.
    - Pliny the Elder – Writings on medicinal herbs.
    - Galen – Developed formulations (Galenicals), basis of pharmacy.

Middle Ages

- Development of alchemy; attempts to convert base metals into gold also led to discovery of new chemicals with medicinal value.
- Paracelsus (1493–1541) – Introduced the concept of "dose makes the poison" and use of chemicals in treatment.

Modern Period

- 19th century – Rapid growth of organic chemistry and isolation of active principles from plants.
    - Morphine (from opium poppy)
    - Quinine (from cinchona bark)
    - Cocaine (from coca leaves)
    - Aspirin (acetylsalicylic acid, synthetic drug)
- 20th century – Development of synthetic drugs and antibiotics:
    - Sulfonamides (first synthetic antibacterial agents)
    - Penicillin (first natural antibiotic discovered by Alexander Fleming, 1928)
    - Insulin (used in diabetes treatment)

Contemporary Medicinal Chemistry

- Involves drug design using computer-aided methods (CADD).
- Use of biotechnology and genetic engineering in drug development.
- Development of targeted therapies (anticancer, antiviral, monoclonal antibodies).
- Nanomedicine and advanced drug delivery systems are new trends.

Steps in Drug Discovery and Development

1. **Identification of new active compounds (Lead discovery)**
    - Screening natural products, synthetic libraries, or designing new molecules.
2. **Modification of structure (SAR studies)**
    - Chemical alterations improve **potency, selectivity, and physicochemical properties**.
3. **Preclinical studies**
    - Laboratory (in vitro) and animal (in vivo) testing for activity, toxicity, metabolism.
4. **Clinical trials**
    - **Phase I** – Safety and dosage in healthy volunteers.
    - **Phase II** – Efficacy in small patient groups.
    - **Phase III** – Large-scale patient testing.
    - **Phase IV** – Post-marketing surveillance.
5. **Optimization of synthesis & formulation**
    - Large-scale production and development of suitable dosage forms.

Ionization

- **Definition:** Ionization is the process by which a molecule exists in ionized (charged) or non-ionized (uncharged) forms depending on its pKa and the pH of the medium.
- **Importance in drug action:**
  - Ionized form: More water-soluble but poorly absorbed through lipid membranes.
  - Non-ionized form: More lipid-soluble, can cross biological membranes and reach target sites.
- **Example:** Weak acids (aspirin) are better absorbed in stomach (acidic pH), while weak bases (morphine) are better absorbed in intestines (alkaline pH).

Solubility

- **Definition:** Ability of a molecule to dissolve in biological fluids (water, gastric fluid, plasma, etc.).
- **Impact:** Directly affects absorption, distribution, bioavailability, and onset of action.
- Poorly soluble drugs may need special formulations (e.g., suspensions, nano-formulations).
- **Methods to improve solubility:**
  1. Structural modification (introducing polar groups, salts).
  2. Use of co-solvents (ethanol, sorbitol, propylene glycol, PEG).
  3. Employing surfactants (sodium lauryl sulfate, polysorbates).
  4. Complexation (with cyclodextrins, inclusion complexes).

Partition Coefficient (P)

- **Definition:** Ratio of a compound's concentration in lipophilic (organic phase, usually octanol) to its concentration in hydrophilic (aqueous phase).

$$P = \frac{[\text{Drug in organic phase}]}{[\text{Drug in aqueous phase}]}$$

- **Significance:**
  - Determines lipophilicity vs hydrophilicity balance.
  - Drugs with high partition coefficient → lipophilic, easily cross membranes but may be poorly soluble in plasma.
  - Drugs with low partition coefficient → hydrophilic, soluble in plasma but poor membrane penetration.
- Ideal drugs have a balanced partition coefficient for optimum ADME.

Hydrogen Bonding

- **Definition:** A dipole–dipole interaction between a hydrogen atom (attached to electronegative atoms like N, O, F) and another electronegative atom with a lone pair.
- **Role in drug action:**
  - Increases water solubility of drugs.
  - Plays a vital role in drug–receptor interactions (enzyme–substrate binding).
- **Types:**
  1. Intermolecular H-bonding → occurs between two different molecules; enhances solubility.
  2. Intramolecular H-bonding → occurs within the same molecule; may decrease solubility but stabilize structure.

Protein Binding

- **Definition:** Reversible interaction between drug molecules and plasma proteins (mainly albumin)

  .

$$Drug + Protein \leftrightarrow Drug\text{–}Protein\ Complex$$

- **Significance:**
  - Only free (unbound) drug is pharmacologically active.
  - Binding influences drug distribution, half-life, and therapeutic effect.
  - High protein-binding drugs may cause drug–drug interactions (e.g., warfarin).
- Protein binding is usually expressed as % of total plasma concentration bound.

Chelation

- **Definition:** Formation of a stable complex between a drug (ligand) and a metal ion using multiple binding sites.
- **Pharmaceutical importance:**
  - Used for detoxification of heavy metals (e.g., EDTA in lead poisoning).
  - Helps in stabilization of drugs (prevent oxidation).
  - Can enhance or reduce absorption of drugs.

Bioisosterism

- **Definition:** Replacement of one atom/group in a molecule with another atom/group having similar size, shape, and electronic properties, while retaining biological activity.
- **Importance:**
  - Improves solubility, potency, selectivity, metabolism, and toxicity profile.
  - Example: Replacement of –H by –F in drugs can increase metabolic stability.
- **Types:**
  1. Classical bioisosteres (atoms/groups with similar valency, e.g., $–CH_3$ and $–NH_2$).
  2. Non-classical bioisosteres (do not obey strict rules but mimic biological effects).

Optical and Geometrical Isomerism

- **Definition:** Existence of molecules with same molecular formula but different spatial arrangements.
- **Types:**
  1. Optical isomerism (enantiomers):
     - Mirror image molecules (chiral).
     - One enantiomer may be active, while the other is less active/toxic.
     - Example: (S)-thalidomide (teratogenic) vs (R)-thalidomide (sedative).
  2. Geometrical isomerism (cis–trans or E–Z):
     - Different orientation of groups across a double bond or ring.
     - Example: Cisplatin (anticancer) is active, while transplatin is inactive.