HUMAN VALUES AND PROFESSIONAL ETHICS

UNIT 1 NOTES

- INTRODUCTION
- PHYSICOCHEMICAL PROPERTIES IN RELATION TO BIOLOGICAL ACTION
- DRUG METABOLISM

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INTRODUCTION

- Medicinal Chemistry is the branch of Chemistry focused on the design, synthesis and development of pharmaceutical compound.
- It combines poinciples from Organic Chemistry, Biochemistry and pharmacology to create new drugs and emprooves exishing ones.

PHYSICOCHEMICAL PROPERTIES IN RELATION TO BIOLOGICAL ACTION

- Physicochemical Properties refers to physical and chemical characteristics of a drug molecule that influence its behaviour in biological systems.
- These properties plays a crucial role in deteomining the drug's absoophion, distribuhion, metabolism and excrehion.
- It includes:

① Ionisation
② Solubility
③ Partition Coefficient
④ Hydrogen Bonding
⑤ Protein Binding
⑥ Chelation
⑦ Bioisosterism
⑧ Optical & Geometrical Isomerism.

① IONISATION

- Ionisation is a key physicochemical property that refers to the ability of a molecule to gain or lose protons (H^+), leading to the formation of charged species (ions).
- The extent of ionization is determined by pka of the drug and pH of the surrounding environment.

RELATION TO BIOLOGICAL ACTION

① Solubility : Ionized drugs are more soluble in water, aiding in dissolution in aqueous environments like gastrointestinal tract.

② Membrane Permeability : Non-ionized forms of drug are more lipophilic, allowing them to cross membranes easily, whereas ionized forms struggle to penetrate lipid bilayers.

③ Absorption & Distribution : Drugs must balance ionization to be absorbed efficiently, weak acids absorb better in acidic environment, while weak bases absorb better in basic environment.

④ Excretion : Ionized drugs are more water soluble and are excreted more easily via the kidneys, while non-ionized drugs may undergo reabsorbtion.

- By understanding Ionization, medicinal chemists can optimize drug properties for better therapeutic action and bioavailibility.

② SOLUBILITY

- Solubility is the ability of a substance (solute) to dissolve in a solvent to form a homogenous solution.
- In the context of Medicinal Chemistry. Drug solubility refers to the extent to which a drug dissolves in biological fluids (e.g. gastric juice, blood or intestinal fluid).
- Drugs must be sufficiently soluble in aqueous fluids to be absorbed, distributed and transported effectively in the body.

BIOLOGICAL SIGNIFICANCE

① Drug Absorption & Bioavailibility :
- A drug must dissolve in GIT fluids before it can be absorbed into the bloodstream.
- Poorly soluble drugs have low dissolution rates, leading to reduced bioavailibility.

② Drug Distribution :
- Once absorbed, a drug circulates in plasma, which mostly water.
- Highly water soluble drugs remains in blood while lipophilic drug distributes over body tissues.

③ Drug Metabolism & Excretion :
- Wates soluble drugs are easily metabolised excreted via kidneys.
- Poorly soluble drugs require metabolism to increase solubility for excretion.

- Solubility is a critical factor in drug design and formulation, affecting absorption, distribution, metabolism and excretion.
- Medicinal Chemists optimize drug solubility to enhance bioavailibility, therapeutic action and patient compliance while minimizing side effects.

③ PARTITION EFFICIENT

- The Partition coefficient is the ratio of compound's concentration in a Lipophilic solvent to its concentration in hydrophilic solvent at equilibrium.
- It is expressed as :

$$P = \frac{[Drug]_{LIPID}}{[Drug]_{WATER}}$$

- The Hydrophilic and Lipophilic nature of ~~log~~ drug is indicated by log P

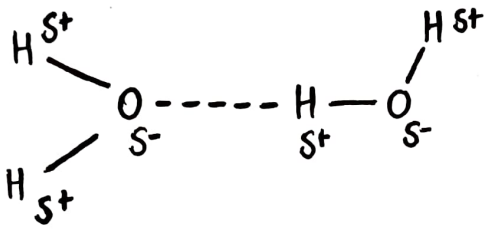
BIOLOGICAL IMPORTANCE

- A moderate log P enhances absorption through biological membranes, as cell membranes are lipophilic.
- Drugs with very high log P are too lipophilic and may become trapped in membranes
- Drugs with very low log P are too hydrophilic and may not cross lipid membranes effectively
- Lipophilic drugs are metabolized in liver before excretion, while hydrophilic drugs are excreted directly by the kidneys.

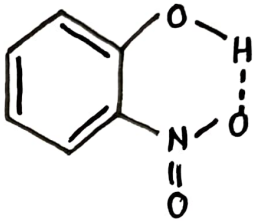
④ HYDROGEN BONDING

- Hydrogen Bonding is a type of weak chemical interaction that occurs when a hydrogen atom (H) is shared between an electronegative donor and an electronegative acceptor.
- It is of two types :

ⓐ Intermolecular Hydrogen Bonding
ⓑ Intramolecular Hydrogen Bonding



Water



O - Nitrophenol

INTERMOLECULAR H-BONDING

IMPORTANCE IN BIOLOGICAL RELATION

① Solubility : Drugs that foom hydrogen bonds dissolve better in water, improving their solubility.
- Example : Paracetamol forms hydrogen bonds, making it highly water-soluble.

② Membrane Permeability : Too many hydrogen bonds make a drug less lipophilic reducing its ability to cross cell membranes.

③ Receptor Binding : Many drug interact with proteins through hydrogen bonds, affecting their potency.

④ Metabolism & Excretion : Hydrogen bonding can influence how drugs bind to liver enzymes for metabolism & how easily they are excreted.

- Hydrogen bonding is essential for drug solubility, absorption, target binding and metabolism.
- Balancing hydrogen bonds is crucial in designing effective drugs.

⑤ PROTEIN BINDING

- Protein Binding refers to the ability of a drug to bind to plasma proteins (such as albumin, α1-acid glycoprotein and lipoproteins) in the bloodstream.
- Drug exist in two forms:

ⓐ Bound Drug (inactive, stored in bloodstream)
ⓑ Free Drug (active, available for biological action)

MAJOR PROTEINS INVOLVED

- Albumin : Binds To Acidic Drugs
- α1-Acid Glycoprotein : Binds to Basic Drugs
- Lipoprotein : Binds to Lipophilic Drugs

IMPORTANCE IN BIOLOGICAL SYSTEM

① Drug Distribution: Highly Protein-bound drug stay in circulation longer and distribute more slowly into tissues.

② Drug Activity: Only the free drug is available to interact with receptors and produce effects.

③ Metabolism & Excretion: Bound drugs are not easily metabolised or excreted. The liver and kidneys primarily remove free drugs.

- Protein binding influences drug distribution, activity, interactions, metabolism and excretion. Understanding it helps in dosing adjustments and avoiding drug interactions.

⑥ CHELATION

- Chelation happens when a drug binds tightly to metal ions like calcium, iron, magnesium or zinc, forming a stable complex.

RELATION WITH BIOLOGICAL SYSTEM

① Affects Absorption : Some drugs bind to metals in food, making them harder to absorb.

② Removes Toxic Metals : Some drugs are used to trap & remove harmful metals from the body.

③ Block Enzymes : Some drugs stop enzymes from working by binding to metals they need.

- Chelation can affect drug absorption, remove toxins & block enzymes.
- Understanding it helps in making drugs work better and avoiding food or metal interaction.

⑦ BIOISOSTERISM

- Befor Discussing, Bioisoterism, let's frost discuss Isosterism.
- Isosterism is the phenomenon where molecules or ions have the same number of atoms and a similar arrangement of electrons, leading to comparable physical and chemical propesties.

Example : N_2 (Nitrogen) and CO (carbon monooxide)

- Both have same number of total electrons (14)
- Both molecules have triple bond b/w two atoms.
- They have similar bond length and ionization energies.

- The concept of isosterism introduced frost by Irving Langmuir in 1919.

BIOISOSTERISM

- Bioisosterism is a concept in Medicinal Chemistry where one funchional group or moleaule is replaced with another that has similar physical and chemical propesties
- This helps improve the drug's effects. reduce side effects or make it last longer in the body.

Detailed Explanation

In drug design, scientist often change parts of a drug to make it better. However if they replace the part with something too different, the drug might stop working. So they use Bioisosteres.

Classification Of Bioisosterism

Bioisosteres are mainly categorized into two main types

① Classical Bioisosteres
② Non- Classical Bioisosteres

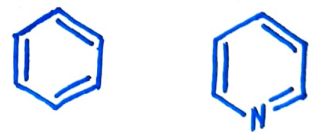
① Classical Bioisosteres

- These are the bioisosteres which have the same valency, shape and electronic properties.
- Example : $-OH$ & $-NH_2$
  $-H$ & $-F$

Classification

They are further classified as follows :

ⓐ Monovalent Bioisosteres : $-OH$ & $-NH_2$
ⓑ Divalent Bioisosteres : $-C=O$ & $-C=S$
ⓒ Trivalent Bioisosteres : $-CH=$ & $-N=$
ⓓ Tetravalent Bioisosteres : $-C$ & $-Si$
ⓔ Ring Equivalents : Benzene & Pyridine



② Non- Classical Bioisosteres

- Non Classical Bioisosteres are those that do not have the same valency or electric properties but still produce similar biological effect.
- Example : Carboxyl ($-COOH$) & Tetrazole ($-C_4H_4N_4$).

SIGNIFICANCE IN BIOLOGICAL RELATION

① Improved Pharmacokinetics: Substituting bioisosteres can enhance a drug's absorption, distribution, metabolism and excretion, leading to better efficacy and stability.

② Reduced Toxicity: Toxic functional groups can be replaced with safer alternatives while maintaining therapeutic effects.

③ Increased Selectivity: Bioisosteric modifications can enhance drug's specificity for its target, reducing side effects.

④ Enhanced Metabolic Stability: Some bioisosteric replacements prevent rapid degradation, prolonging drug's half life.

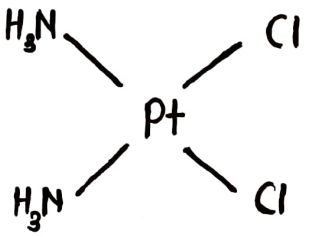
⑧ GEOMETRICAL ISOMERISM

- Geometrical Isomers are stereoisomerism that have a different arrangement of groups or atoms around double bonds.
- They are of two types :

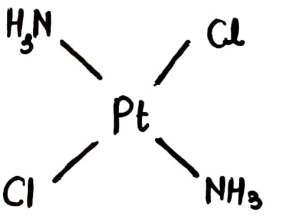
ⓐ Cis- Isomer
ⓑ Trans- Isomer

RELATION TO BIOLOGICAL ACTION

- Geometrical Isomers can have different biological activities.
- For Example : Cis-platin is an effective anticancer drug, while trans-platin is inactive.



Cis- Platin



Trans- Platin

⑨ Optical Isomerism

- Optical Isomerism occurs when molecules have the same chemical formula but exist in two- mirror image forms.
- It is of two types :

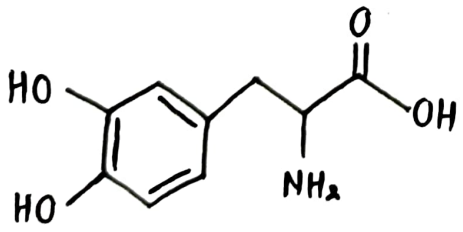
ⓐ Dextrorotatory
ⓑ Levorotatory

ⓐ Dextrorotatory : Rotates plane polarised light

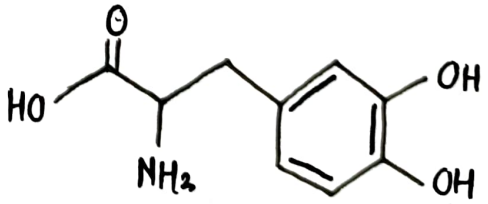
ⓑ Levorotatory : Rotats plane polarised light to

Optical Isomerism In Relation To Biological Action

- Optical Isomers can have drastically different effect in biological system
- For Example : L- Dopa is used to treat parkinson's disease while D- Dopa is biologically active.



L - Dopa



D - Dopa

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

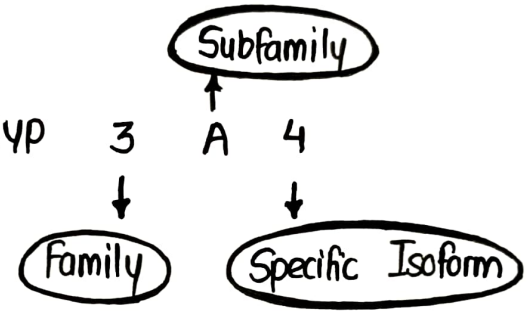
Metabolism usually leads to conversion of :

- 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%).

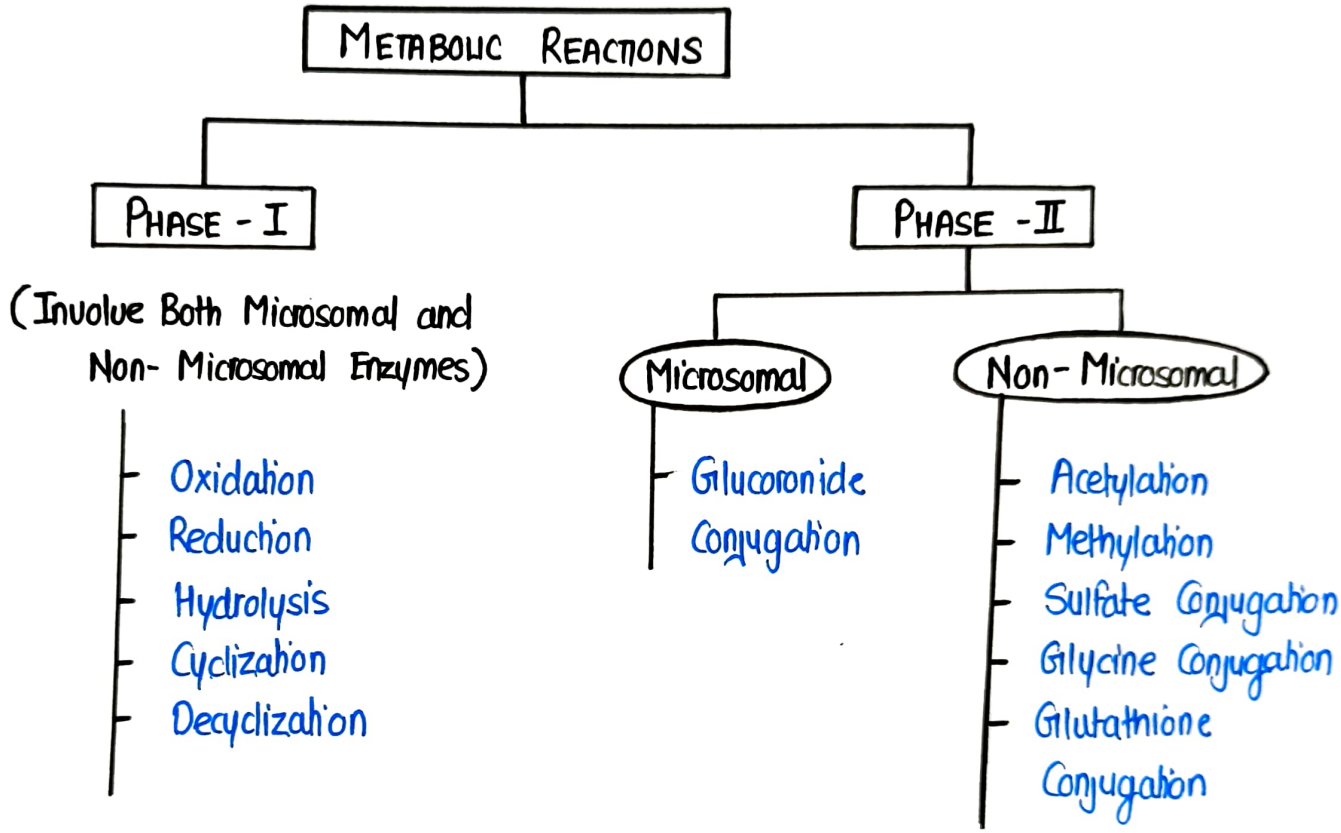
Example Of CYP Enzymes

- 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 & 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.

② PHASE II REACTIONS

- Phase II Reactions are also known as Conjugation Reactions
- These reactions attach polar groups (e.g. glucaronic 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.

THANK YOU

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