St Peter's Institute of Pharmaceutical Sciences

Course : Bachelor of Pharmacy

Subject : Medicinal Chemistry I

Subject Code: BP402T

Physiochemical properties.

The ability of a chemical compound to elicit a pharmacological/ therapeutic effect is related to the influence of various physical and chemical (physicochemical) properties of the chemical substance on the bio molecule that it interacts with.

1) Physical Properties: Physical property of drug is responsible for its action

2) Chemical Properties: The drug react extracellularly according to simple chemical reactions like neutralization, chelation, oxidation etc.

Various Physico-Chemical Properties are

1. Solubility
2. Partition Coefficient
3. Dissociation constant
4. Hydrogen Bonding
5. Ionization of Drug
6. Redox Potential
7. Complexation
8. Surface activity
9. Protein binding
10. Isosterism

1.Solubility: The solubility of a substance at a given temperature is defined as the concentration of the dissolved solute, which is in equilibrium with the solid solute. Solubility depends on the solute and solvent as well as temperature, pressure, and pH. The solubility of a substance is the ratio of these rate constants at equilibrium in a given solution. The solubility of an organic medicinal agent may be expressed in terms of its affinity/philicity or repulsion/phobicity for either an aqueous (hydro) or lipid (lipo) solvent.

^{K}SOLUBILITY= ^{K}SOL/^{K}PPT

The atoms and molecules of all organic substances are held together by various types of bonds (e.g. London forces, hydrogen bonds, dipole-dipole, etc.). These forces are intricately involved in solubility because it is the solvent-solvent, solute-solute, and solvent-solute interactions that govern solubility.

Methods to improve solubility of drugs

1) Structural modification (alter the structure of molecules)
2) Use of Cosolvents (Ethanol, sorbitol)
3) Employing surfactants
4) Complexation

Importance of solubility

1) Solubility concept is important to pharmacist because it govern the preparation of liquid dosage form and the drug must be in solution before it is absorbed by the body to produce the biological activity.
2) Drug must be in solution form to interact with receptors.

2.Partition coefficient: The ability of a drug to dissolve in a lipid phase when an aqueous phase is also present, often referred to as lipophilicity. The lipophilicity can be best characterized by partition coefficient. Partition coefficient can be defined as the equilibrium constant of drug concentrations for "unionizable" molecules in the two phases.

$$P = \frac{[drug]_{lipid}}{[drug]_{water}}$$

and for "ionizable" molecules (acids, bases, salts), where alpha (α) is the degree of ionization in aqueous solution. It is basically a constitutive property.

$$P = \frac{[drug]_{lipid}}{(1-\alpha)[drug]_{water}}$$

Naturally, the partition coefficient is one of the several physicochemical parameters influencing drug transport and distribution. The contribution of each functional groups and their structural arrangement help to determine the lipophilic or hydrophilic character of the molecule. Partition coefficient majorly influence drug transport characteristics; the way in which the drugs reach the site of action from the site of application (e.g. injection site, gastrointestinal tract, and so forth). Since the blood distributes drugs, they must penetrate and traverse many cells to reach the site of action.

Factors affecting Partition Co-efficient

1) pH
2) Co solvents
3) Surfactant
4) Complexation

Importance of partition coefficient

1) It is generally used in combination with the Pka to predict the distribution of drug in biological system.
2) The factor such as absorption, excretion & penetration of the CNS may be related to the log P value of drug.
3) The drug should be designed with the lowest possible
4) Log P, to reduce toxicity, nonspecific binding &bioavailability.

3.Ionization of drug: The accumulation of an ionized drug in a compartment of the body is known as"ion trapping". The ionization of a drug is dependent on its pKa and the pH. The pKa is the negative Logarithm of Ka. The Ka is the acidity constant of a compound, its tendency to release a proton. The ratio of ionized/ non ionized drug may be determined by the Henderson- Hasselbalch relationship. This may be used to derive an Effective partition coefficient : Ex: Phenobarbital pKa is 7.4. It is evident that phenobarbital would be predominantly in the unionised form in acidic environment.

$$pH - pK_a = \log([A^-]/[HA])$$

$$= \log([\text{ionized}]/[\text{non ionized}]) \quad \text{for acids}$$

$$pH - pK_a = \log([B]/[HB^+])$$

$$= \log([\text{non ionized}]/[\text{ionized}]) \quad \text{for bases}$$

$$\text{Fraction non-ionized} = [HA]/([HA]+[A^-])$$

$$= 1/1 + ([A^-]/[HA])) = 1/(1 + \text{antilog}(pH - pK_a))$$

Importance of ionisation of drugs

1) The lower the pH relative to the pKa greater is the fraction of protonated drug (protonated drug may be charged or uncharged)

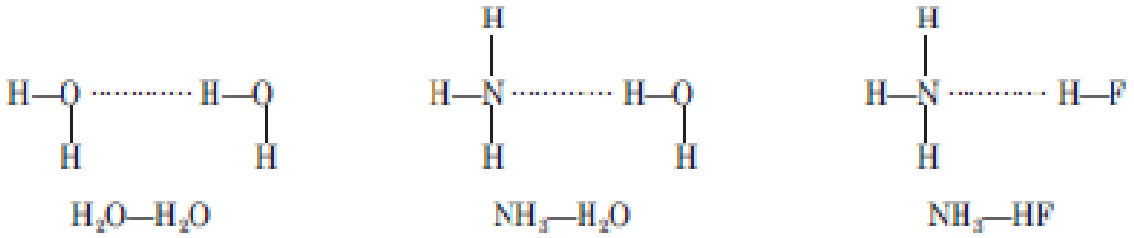
2) Weak acid at acidic pH : more lipid-soluble, because it is uncharged—the uncharged form more readily passes through biological membranes. Note that a weak acid at acidic pH will pick up a proton and become uncharged.

$$RCOO+H \longrightarrow RCOOH$$

3) Weak base at alkaline pH : more lipid-soluble, because it is uncharged—the uncharged form more readily passes through biological membranes. Note that a weak base at more alkaline pH will lose a proton, becoming uncharged

$$RNH_3 \longrightarrow RNH_2+H^+$$

4. Hydrogen Bonding: The hydrogen bond is a special type of dipole-dipole interaction between the hydrogen atom in a polar bond such as N—H, O—H,or F—H and an electronegative atom O, N, or F atom. This interaction is written as A—H····· B. A and B represent O, N or F. A—H is one molecule (or) part of a molecule and B is a part of another molecule; and the dotted line represents the hydrogen bond. These three atoms usually lie along a straight line, but the angle AHB can deviate as much as 30° from linearity. Ex: Hydrogen bonding in NH_3, H_2O and HF.



Generally the hydrogen bonding is classified into 2 types
a) Intermolecular hydrogen bonding
b) Intramolecular hydrogen bonding

(A) Intermolecular hydrogen bonding. In this type, hydrogen bonding occurs between two or more than two molecules of the same compound and results in the formation of polymeric aggregate. Intermolecular hydrogen bonding increases the boiling point of the compound and also its solubility in water. The molecules that are able to develop intermolecular hydrogen bonding improve their solubility by the formation of intermolecular hydrogen bonding with water. Ex: Ethanol shows higher boiling point and higher solubility in water than dimethyl ether even though both have the same molecular weight.
(B) Intramolecular hydrogen bonding. In this type, hydrogen bonding occurs with in two atoms of the same molecule. This type of hydrogen bonding is commonly known as chelation and frequently occurs in organic compounds. Sometimes intramolecular hydrogen bonding develops a six or 5-membered ring. Ex:o-chlorophenol,o-nitro phenol.
Intramolecular hydrogen bonding decreases the boiling point of the compound and also its solubility in water. This is because of the fact that the chelation between the ortho substituted groups restricts the possibility of intermolecular hydrogen bonding with water and thus prevents association of the molecules, which would have raised the melting point, boiling point. o-Nitrophenol.-215°C,p-Nitrophenol-279°C,m-Nitrophenol-279°C.

Effects of hydrogen bonding. Almost all physical properties are affected by hydrogen bonding. Here only those properties that are prominently altered such as boiling points, melting point, water solubility etc., are discussed. In addition to physical properties several chemical properties like acid character, basic character, properties of carbonyl group are also affected by hydrogen bonding.

5. Protein binding
The reversible binding of protein with non-specific and nonfunctional site on the body protein without showing any biological effect is called as protein binding.

Protein + drug $\longleftrightarrow$ Protein-drug complex

Depending on the whether the drug is a weak or strong acid, base or is neutral, it can bind to single blood proteins to multiple proteins (serum albumin, acid-gycoprotien or lipoproteins). The most significant protein involved in the binding of drug is albumin, which comprises more than half of blood proteins. Protein binding values are normally given as the percentage of total plasma concentration of drug that is bound to all plasma protein.

Free drug(Df) + Free protein(Pf) $\longleftrightarrow$ Drug /protein complex (Dp)

Total plasma concentration (Dt) = (Df) + (Dp)

6. Complexation or chelation:-Complexes or coordination compounds result from a donor acceptor mechanism (donating accepting electron or, rather, an electron pair) or Lewis acid-base reaction (donating-accepting protons). Any non-metallic atom or ion, whether free or contained in a neutral molecule or in an ionic compound, that can donate an electron pair, may serve as the donor. The acceptor, or constituent that accept the pair of electrons, can be a metallic ion or sometimes also a neutral molecule. In addition to "coordinate covalence" (i.e., bonds formed by the classical electron donor-acceptor mechanism), intramolecular forces can also be involved in the formation of complexes. Complexes may be divided broadly into two classes depending on whether the acceptor compound is a metal ion or an organic molecule.
The compounds that are obtained by donating electrons to metal ion with the formation of a ring structure are called chelates. The compounds capable of forming a ring structure with a metal atom are termed as Ligands. Most of the metals are capable of forming chelates or complexes (if the metal is not in a ring, the compound is called a metal complex), but the chelating property ís restricted to atoms like N, O and S, which are electron donating.

Applications of chelation
The phenomenon of chelation ís significantly involved in biological system and to some extent in explaining drug action.
1) Dimercaprol is a chelating agent. It is an effective antidote for organic arsenical, Lewisite, but can aleo be used for treatment of poisoning due to antimony, gold and mercury.
2) Penècillamine is an effective antidote for the treatment of copper poisoning because it forms water-soluble theist. with copper and other metal ions.
3) 8-hydroxyquinoline and its analogs act as antibacterial and antifungal agents by complexing with iron or copper.

Bioisosterism

Bioisosterism is defined as compounds or groups that possess near or equal molecular shapes and volumes, approximately the same distribution of electron and which exhibit similar physical properties.

They are classified into two types.,

i) Classical biososteres

ii) Non classical bioisosters.

1. Classical Bioisosteres: They have similarities of shape and electronic configuration of atoms, groups and molecules which they replace. The classical bioisosteres may be,

A). Univalent atoms and groups:

i) Cl, Br, I

ii) CH3, NH2, -OH, -SH

B).Bivalent atoms and groups:

i) R-O-R,R-NH-R, R-S-R, RCH2R

ii) –CONHR, -COOR, -COSR

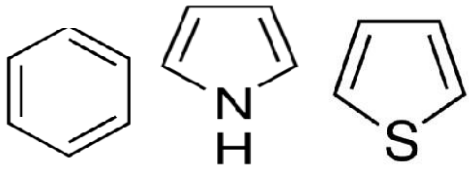
C).Trivalent atoms and groups:

i)-CH=, -N=

ii) –p=, -AS=

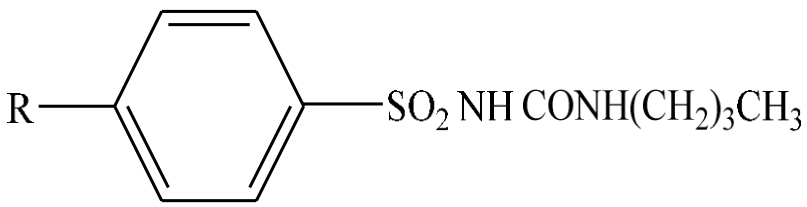
D).Tetravalent atoms and groups: =c=, =N=, =P=

E).Ring equivalent: -CH=CH-, -S-, -O-, -NH, -CH2-



Application of Classical Bioisosteres in drug design

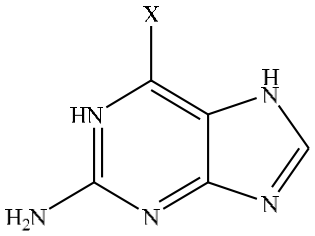
i) Replacement of –NH 2 group by –CH3 group



Carbutamide R= NH2

Tolbutamide R= CH3

ii)Replacement of –OH & -SH



Guanine= -OH
6-Thioguanine = -SH

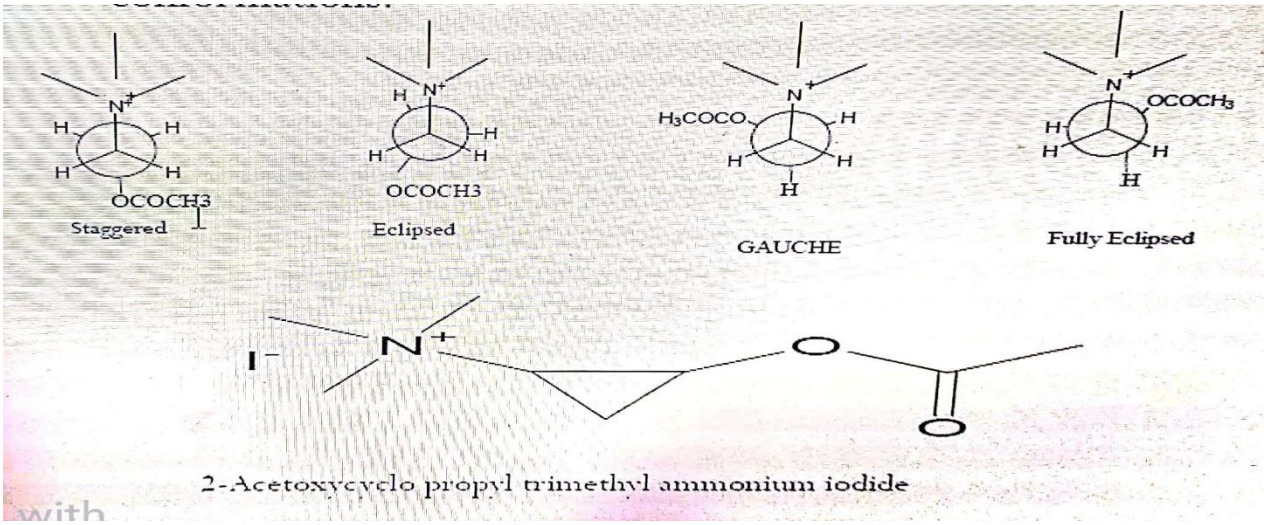
2. Non classical Bioisosteres: They do not obey the stearic and electronic definition of classicalisosteres.Non-classical biosteres are functional groups with dissimilar valence electron configuration. Specific characteristics are

a) Electronic properties
b) Physicochemical property of molecule
c) Spatical arrangement
d) Functional moiety for biological activity.

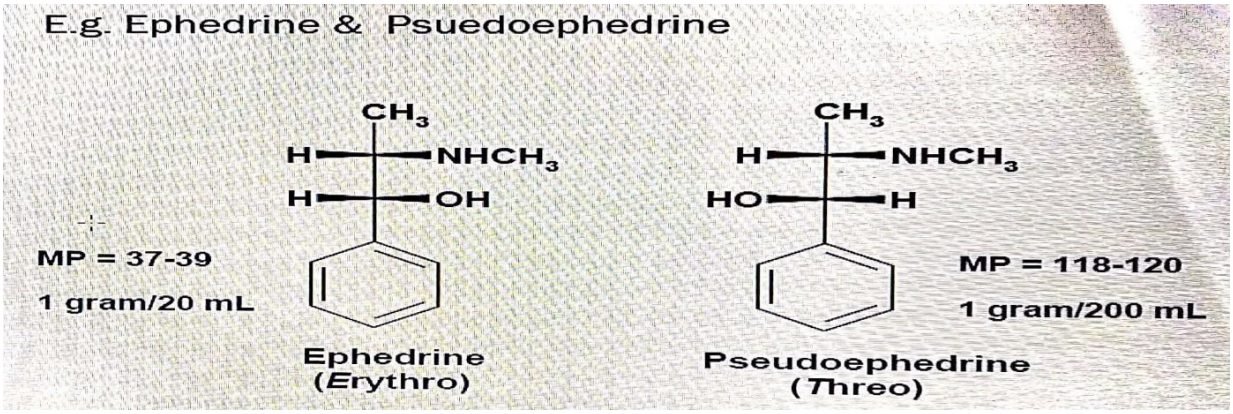
Examples: Halogens Cl, F, Br, CN
Ether -S-, -O-
Carbonyl group
Hydroxyl group –OH, -NHSO2R, CH2OH
Catechol

Stereochemistry of drugs: Stereochemistry involve the study of three dimensional nature of molecules. It is study of the chiral molecules. Stereochemistry plays a major role in the pharmacological properties because;
1. Any change in stereo specificity of the drug will affect its pharmacological activity
2. The isomeric pairs have different physical properties (log p, pKa etc.) and thus differ in pharmacological activity.
The isomer which have same bond connectivity but different arrangement of groups or atoms in the space are termed stereoisomer.

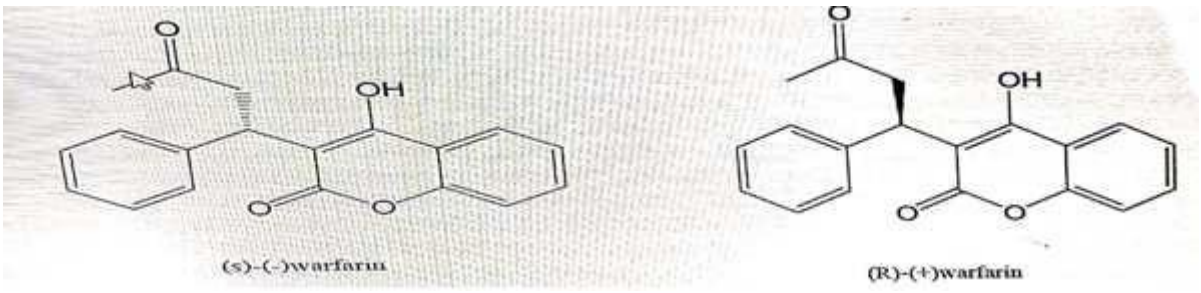
Conformational Isomers: Different arrangement of atoms that can be converted into one another by rotation about single bonds are called conformations. Rotation about bonds allows inter conversion of conformers.
A classical example is of acetylcholine which can exist in different conformations



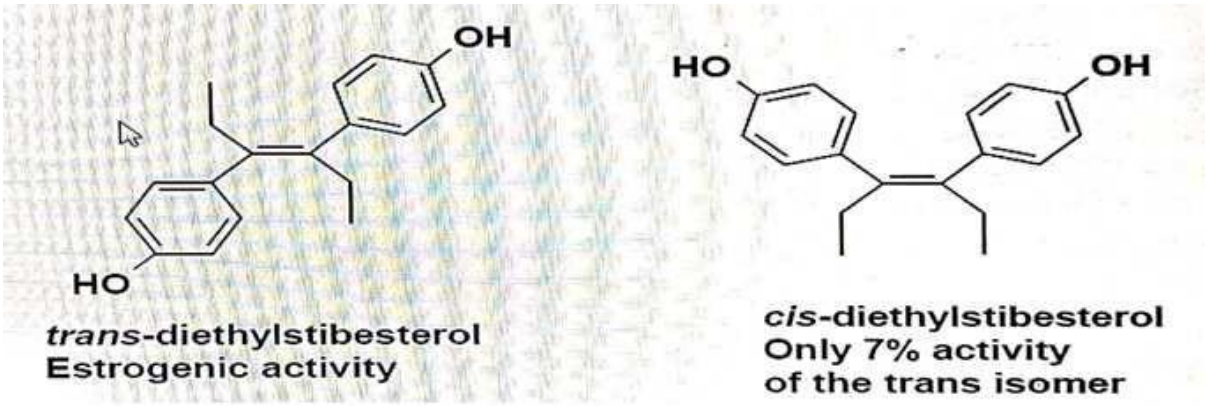
Optical Isomers: Stereochemistry, enantiomers, symmetry and chirality are impotant concept in therapeutic and toxic effect of drug. A chiral compound containing one asymmetric centre has two enantiomers. Although each enantiomer has identical chemical & physical properties, they may have different physiological activity like interaction with receptor, metabolism & protein binding. A optical isomers in biological action is due to one isomer being able to achieve a three point attachment with its receptor molecule while its enantiomer would only be able to achieve a two point attachment with the same molecule.



The category of drugs where the two isomers have qualitatively similar pharmacological activity but have different quantitative potencies.



Geometric Isomerism: Geometric isomerism is represented by cis/trans isomerismresulting from restricted rotation due to carbon-carbon doublebond or in rigid ring system.



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