UNIT-1

Introduction

In Medicinal Chemistry, we study about the invention, discovery, design, identification and preparation of biologically active compounds, their metabolism, mode of action and the structure-Activity relationships (SAR).

History

→ In early civilisations of Egypt, India and China, the plants being used to treat various diseases.

→ In the beginning of 19th century, the isolation of a no. of alkaloids like:

Morphine — 1803
Quinine — 1823
Atropine — 1833

was used in medicinal chemistry.

→ In 1860 :- synthesis of synthetic/semi-synthetic derivatives of the plant origin like:

Benzocaine from cocaine (1892)
Aspirin from salicin (1899)

→ 1890-1940 :- 1st Phase of Modern Medicinal Chem. The development of effective dreegs for the treatment of Tuberculosis, Typhoid, Malaria, etc.

→ In 1936 — Sulphonamide

→ 1940 — Penicillin antibiotic

→ 1949 — Chloremphenicol and Tetracycline

→ 1945-65 :- Golden Era

1949 — corticosteroids
1950 — Antipsychotics
1955 — Anti-depressants
1957 — Hypoglycemic
1959 — Contraceptives
1960 — Benzodiazepines

Physicochemical Properties in Relation to Biological Action

Biological action of a drug molecule is dependent on its physicochemical (physical + chemical) characteristics.

Physicochemical properties that influence the pharmacological action of medicinal agents are:

(1) Ionisation
(2) Solubility
(3) Partition coefficient
(4) Hydrogen bonding
(5) Protein binding
(6) Chelation
(7) Bioisosterism
(8) Optical and Geometrical Isomerism

Ionisation

Ionised form of drug has a better solubility in water which is essential for absorption. During systemic (in blood) absorption of drug, the nature of drug should be hydrophilic which is possible in ionised form.

Ionisation is dissociation of ions of a salt.

For example,

$$NaCl \longrightarrow \underset{\text{(ionised)}}{Na^+} + \underset{\text{(ionised)}}{Cl^-}$$

(unionised)

But, during distribution of drug into the body. It has to cross various biological membranes (cell membranes) which is a phospholipid bilayer. So, to cross the cell membranes, the drug should be in unionised state (lipophilic).

The degree of ionisation can be calculated by Henderson-Hasselbalch equation:

For an acid → $pH = pKa + \log\left[\frac{\text{Ionised conc.}}{\text{Unionised conc.}}\right]$

For base → $pH = pKa + \log \frac{[\text{Unionised drug conc.}]}{[\text{Ionised drug conc.}]}$

Solubility

The solubility of a substance at given temperature is defined as the maximum amount of particles of that substance that can be dissolved 100ml of solvent. Solubility of solute in the solvent depend highly on the interactions in particles (solvent-solvent particles, solute-solute particles and solvent-solute particles).

Methods of solubility improvement:

- structural modification
- Use of co-solvents
- Employing surfactants
- Complexation

→ A good solubility of drug means that its bioavailability will be higher.

→ A drug in solution form is absorbed easily.

Partition Coefficient

Partition coefficient is the ratio of drug concentration in two phases which are at equillibrium.

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

→ Highly water soluble drugs cannot penetrate organs which are rich in lipid content such as brain. On the other hand, a lipophilic (fat-loving) drug will not leave the fat tissue quickly to reach the target.

→ Partition coefficient plays this role of balancing this hydrophilic or lipophilic nature of drug, thereby affecting the drug absorption and distribution.

→ Partition coefficient tells about the nature of drug:

$P > 1 \implies$ lipophilic more

$P < 1 \implies$ hydrophilic more

Hydrogen Bonding

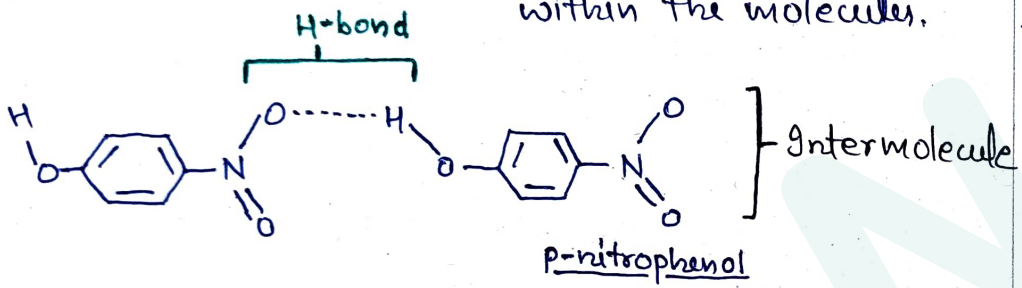
In a hydrogen bond, hydrogen atom holds two other atoms together. This bond is formed between hydrogen and electronegative atoms. The atoms which can form H-bonds carry at least an unshared pair of electrons, like F, O and N.

The atoms forming H-bond to a lesser extent are Cl and S.

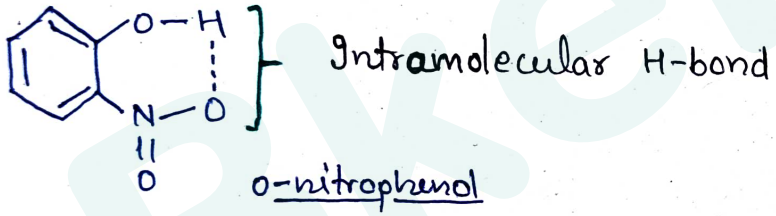
Hydrogen-bonding can be classiffied as:

(1) Intermolecular H-bonding :- This H-bonding occurs b/w two or more molecules.

(2) Intramolecular H-bonding :- H-bonding occurs within the molecules.



p-nitrophenol



o-nitrophenol

→ Intermolecular bonds are weaker than the intramolecular bonds.

→ Having multiple H-bonding increases aqueous solubility of drug, hence the drug molecules reach the target site on receptors with minimal aqueous solubility.

→ H-bonding alters the physical, chemical and biological properties of compounds significantly.

Protein Binding

→ The distribution, elimination and its pharmacological effect of a drug is affected by their binding to blood proteins.

→ Due to high molecular weight of proteins, they cannot pass through capillaries and due to their low solubility in lipids, they cannot cross the cell membranes.

→ Drugs cannot pass through cell membranes if they are bound to plasma proteins, affecting the drug distribution.

→ However the unbound drug freely circulates and passes through the cell membranes and undergoes glomerular filtration.

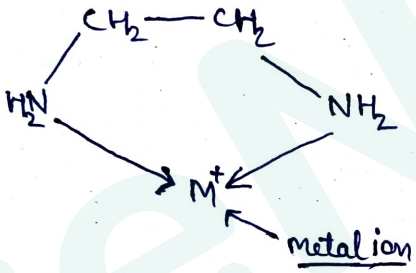
→ As a general rule, agents (drugs) that are minimally protein bound penetrate the tissues better than those that are highly bound.

→ Albumin comprises of nearly 50% of total plasma protein bindings with drug.

Chelation

The compounds that are capable of forming a ring structure with metal ion are called ligands.

The reversible binding (or complexation) of a ligand to a metal ion to form a chelate is called chelation.



chelates donate electrons to the metal ion.

Ligands having more than one electron donating groups are called chelating agents.

→ Most of the metals can form chelates or complexes. But the chelating property is restricted to atoms like N, S, O which are electron donating.

→ Penicillamine is an effective antidote in copper poisoning

→ Complexation (or chelation) reduce the rate of absorption of drug but does not affect the availability of drug.

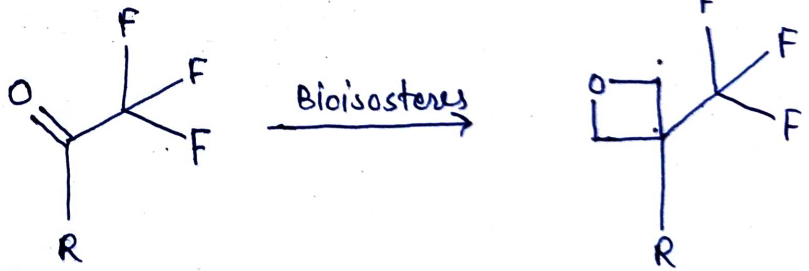
→ Calcium + EDTA form complex which increase the permeability of membrane.

Bioisosterism

Bioisosteres are compounds or groups that have almost equal molecular shapes, volumes and equal electron distribution and similar physical characteristics with similar biological activity.

e.g. CO_2 & NO_2 and N_3^- & NCO^-.

Also, a bioisostere is a molecule formed from the exchange of an atom or a group of atoms with an alternative molecule with similar atom or group of atoms. The objective of forming a bioisostere is to create a new molecule with similar biological properties to the parent compound.



Classification of Bioisosteres

(1) Classical Bioisosteres :- similar valence electron configurations.

e.g. O & S.

There may be:

a) Monovalent atoms or groups:

OH, NH_2, CH_3, Cl, F, H, SH, PH_2

b) Bivalent atoms or groups

$-CH_2-$, $-NH-$, $-O-$, $-S-$, $-CONHR$

(c) Trivalent

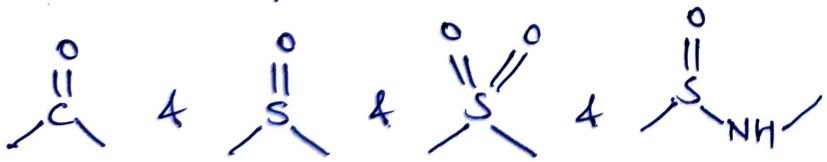
$-CH=$, $-N=$, $-P=$, $-As=$

(d) Tetravalent

(2) Non-classical Bioisosteres : dissimilar valence electron configuration.

e.g. tetrazole & carboxylate

Carbonyl groups



Optical Isomers

Optical isomers are the compounds which have same molecular and structural formula and also similar properties but differ in their behavior towards light.

They differ in their ability to rotate plane polarized light (PPL).

→ They may rotate light either in clockwise direction or anticlockwise direction.

If clockwise → (+) dextrorotatory

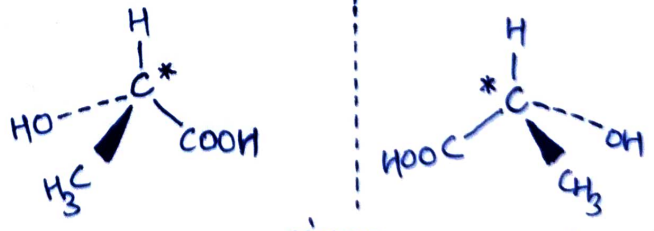
anticlockwise → (−) levorotatory

→ Optical isomers may of following types:

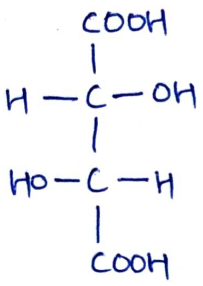
(i) Enantiomers → they are mirror images which are non-superimposable.

(ii) Diasteriomers → They are neither mirror images nor superimposable.

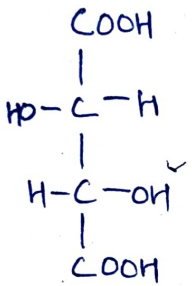
Enantiomers



(+) Lactic acid (−) Lactic acid



(+)-tartaric acid



(−)-tartaric acid

Diastereomers

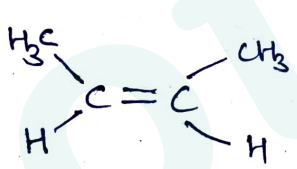
Biological activity of Optical Isomers

→ The bronchodilator activity of (−)-isoprenaline is way more than that of (+)-isoprenaline.
→ The vasoconstrictor activity of (−)-epinephrine is 12-15 times more than (+)-epinephrine.
→ (+)-penicillamine is used in the treatment of arthritis while (−)-penicillamine is toxic.

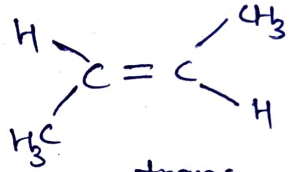
Geometrical Isomerism

Geometrical isomers are those which have same number and types of atoms and bonds but have different spatial arrangement (geometry). This is also known as cis-trans isomerism.

An isomer is cis-isomer when the identified groups are attached on the same side of the plane of the molecule and trans-isomer when attached on opposite sides of it.



cis



trans

Biological activity

→ The estrogenic activity of trans-isomer of diethylstilbestrol is 14 times more than its cis-isomer.
→ The correlation or similarity between geometrical isomerism and their biological activity is of little importance due to the different physical properties of geometrical isomers.

Drug Metabolism

→ The chemical alteration of a drug by the body is called drug metabolism, which is also known as biotransformation.

→ Once a drug enters the human body, it undergoes metabolism and yields metabolic products (metabolites) which are either inactive or similar or different from original drug in terms of therapeutic activity.
These metabolic products are excreted out of body.

→ Some drugs are administered in an inactive form which on metabolism yields active forms producing the desired therapeutic effects. Such drugs are called prodrugs.

→ During metabolism of drug, the lipid soluble soluble drug is converted to water soluble drug to avoid reabsorption in renal tubules and help in excretion.

→ The last destiny of the drug is that it is excreted out of the body.

Sites for Drug Metabolism

→ Though every biological tissue possess some ability to metabolise drugs, the principal organ for metabolism is the smooth endoplasmic reticulum within the liver cells.

→ Cytochrome P450 enzymes are the group of metabolising enzymes present in liver which metabolises most of the drugs.

→ The following factors which make liver the primary organ for drug metabolism:
(1) Its large size
(2) Chemicals absorbed, first enters the liver
(3) The concentration of most drug-metabolising enzyme systems is high in liver.

→ other sites for drug metabolism:
(1) Epithelial cells of GIT
(2) Lungs
(3) Kidneys
(4) Skin

Enzymes for Drug Metabolism

(A) Enzymes involved in Phase-I Metabolism

(1) Oxidation
- (a) Cytochrome P_{450} mono-oxygenase system
- (b) Flavin-containing mono-oxygenase system
- (c) Alcohol dehydrogenase & aldehyde dehydrogenase
- (d) Monoamine oxidase (MAO)
- (e) Co-oxidation by peroxidase

(2) Reduction
- (a) NADPH - cytochrome P_{450} reductase
- (b) Reduced (ferrous) cytochrome P_{450}

(3) Hydrolysis
- (a) Esterase and amidase
- (b) Epoxide hydrolase.

(B) Enzymes involved in Phase-II Metabolism

(1) Methylation → Methyltransferase

(2) Sulphation

Glutathione S-transferases and sulfotransferases.

(3) Acetylation → N-acetyltransferases and Amino-acid N-acyl transferases.

(4) Glucuronidation → UDP-glucuronosyltransferases

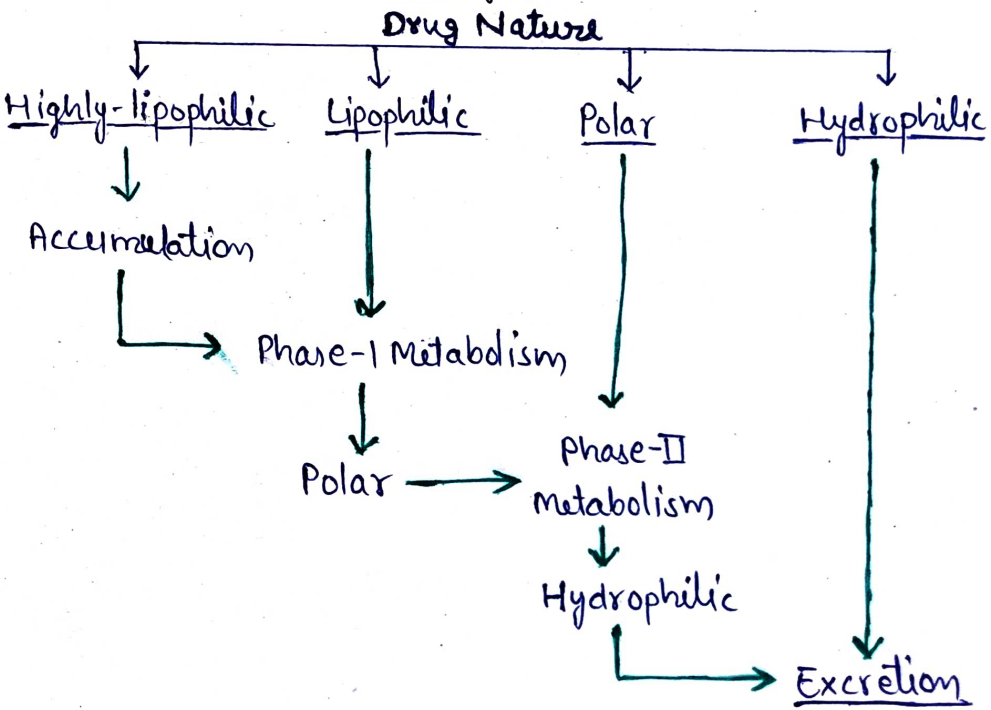
Drug Metabolism Principles

The entire process of metabolism occurs in two phases:

(1) Phase-I :- Metabolism / non-synthetic phase

(2) Phase-II :- Synthetic reaction.

Metabolism Pathways



Phase-1 Reaction

This is the first phase of metabolism when the drug enters the metabolic pathway. It is the predominant pathway of biotransformation. The most common phase-1 reactions are oxidation, Reduction and hydrolysis.

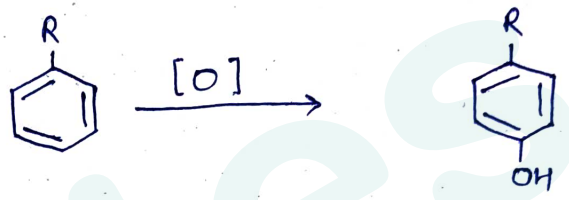
Ⓐ Oxidation

Oxygen reactions involve the loss of electrons. Most of these reactions are catalysed by the enzymes called mono-oxygenases or mixed-function oxidases (mfo) or cytochrome P_{450}. oxidation involves the addition of oxygen into substrate (X) and reduction of second atom of oxygen into water using a reductant (RH_2).

$$X + RH_2 \xrightarrow{O_2} X{-}O + H_2O + R$$

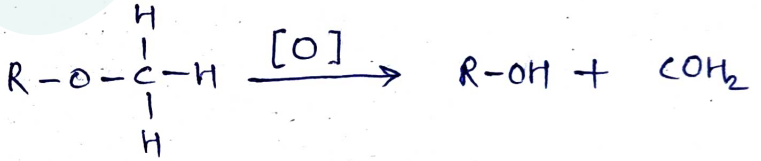
> Phase-1 reactions convert a parent drug to more polar (water-soluble) active metabolites by inserting a polar functional group (-OH, $-NH_2$).

1) Aromatic hydroxylation



2) Dealkylation → removing of alkyl groups from a compound.

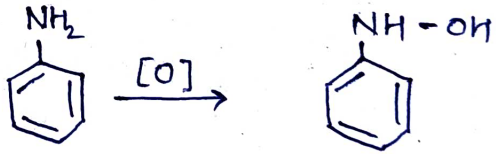
for oxygen atom



for nitrogen atom

$$R\,NHCH_3 \xrightarrow{[O]} RNH_2 + CH_2O$$

2) N-oxidation



★ Metabolites are the products of metabolism processes (or reactions or metabolic pathways.

Ⓑ Reduction → This involves the introduction of hydrogen.

(1) Nitro-reduction

$$RNO_2 \longrightarrow RNH_2$$

chloremphenicol is reduced to arylamine.

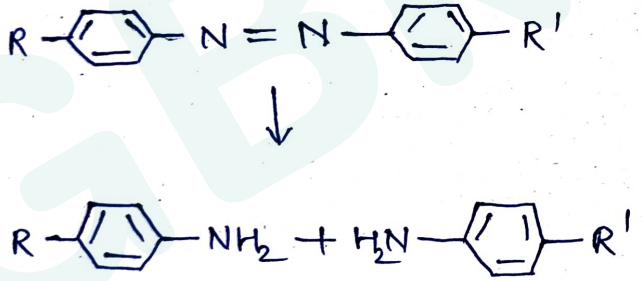
(2) Keto-Reduction

$$RCOR' \longrightarrow R-\overset{OH}{\underset{|}{C}}H-R'$$

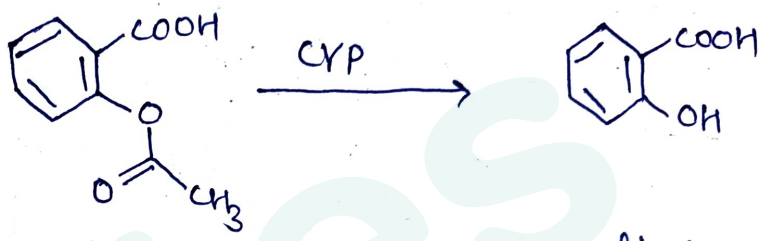
cortisone to hydrocortisone reduction

(3) Azo reduction

e.g. Prontosil to sulfanilamide



Ⓒ Hydrolysis → In this process, the drug molecule is broken down into smaller molecules by the addition of a water molecule (H_2O).



Aspirin — salicylic acid

Ⓓ Cyclisation → The process results in the formation of ring structure from compounds that are arranged in straight chain, e.g. proguanil.

Ⓔ Decyclisation → In this process, the ring structure of the cyclic drug molecule opens up, e.g., phenytoin, barbiturate.

Phase-II Reactions

Also known as 'synthetic reactions', or 'conjugation reactions', which generally serves as the detoxifying step in metabolism of drugs.

Xenobiotics → These are the chemicals to which an organism is exposed, that are external to the normal metabolism of the body. Without metabolism many xenobiotics would cause toxicity in the body.

Phase-II reactions convert a parent drug to more polar inactive metabolites by conjugation of subgroups to -OH, -SH, $-NH_2$ functional groups on a drug.

1) **Conjugation with Glucuronic Acid**

→ conjugates with -OH and -COOH derived from glucose in presence of enzyme UDP glucuronyl transferases.

$$\text{Drug} + \text{UDPGA} \xrightarrow{\text{Microsomal glucuronyl transferase}} \text{Drug glucuronide} + \text{UDP}$$

example of drugs

Aspirin, paracetamol, PABA, Morphine

(2) **Acetylation**

Drugs with amino or hydrazine groups are metabolised like hydralazine, dapsone, procainamide, sulphonamides.

$$R\text{-}NH_2 \xrightarrow[\text{Acetyl CoA}]{\text{N-acetyl transferase}} R\text{-}NHCOCH_3$$

Factors Affecting Drug Metabolism

A variety of factors may affect the activities of the enzymes involved in metabolizing drugs.

1. **Chemical Factors**

- Enzyme Induction
- Enzyme Inhibition
- Environmental chemicals

2. **Biological Factors**

- Age, diet, sex differences
- Species differences
- Strain differences
- Altered physiological factors

Enzyme Induction

Enzyme induction is defined as a higher amount or increased activity of enzymes that occurs by the presence of an exogenous substance (in this case, a drug).

Mechanisms that leads to enzyme induction:

- Increase in both liver size and liver blood flow.
- Increase in total protein content
- Increased stability of enzymes

Consequences of enzyme induction include:

→ decrease in pharmacological activity of drugs

→ Altered physiological status due to enhanced metabolism of endogenous compounds like sex hormones. Example—

Oral contraceptive steroids —CYP3A4→ Inactive, excreted

Induction ↑

Rifampicin

Enzyme Inhibition

A decrease in the drug-metabolizing activity of an enzyme is called enzyme inhibition.

Example of enzyme inhibition:—

Terfenadine —→ Active antihistamine

Inhibition ↑

Erythromycin
Ketoconazole

Environmental Chemicals

- DDT and polycyclic aromatic hydrocarbons contained in cigarette smoke have enzyme induction effect.
- Organophosphate insecticides and heavy metals like mercury, nickel show inhibition effect.
- Other environmental factors are: temperature, altitude, pressure, atmosphere, etc.

Biological Factors

Age

→ In neonates (upto 2 months) and in infants (2 months to 1 year), the microsomal enzyme system is not fully developed. So, many drugs are metabolised slowly.

→ Children below 12 years have metabolic rate higher than adults, hence large mg/kg dose is required.

→ Enzyme activity is reduced due to the reduced liver size.

Diet

- low protein diet decreases and high protein diet increases the drug metabolizing ability of enzymes.
- Grapefruit inhibits metabolism of many drugs.
- starvation results in decreased amount of glucuronides than under normal conditions.

→ Fat-free diet depresses P-450.

Sex

Drug metabolizing ability in females is less.

Species→ some metabolizing enzymes are present only in a few mammalian species and are absent in humans.

Thus, drugs metabolized by these enzymes prove to be toxic to humans, while they are non-toxic to others.

For example– enzyme atropinase is present in rabbits and is absent in humans. Therefore, atropine is non-toxic to rabbits but toxic to humans.

Genetic

Certain individuals may inherit drug-metabolizing enzyme deficiency.

Body temperature

Rise in temperature enhances drug metabolism while decrease in temperature reduces it.

Altered Physiological Factors

- Pregnancy is known to affect hepatic metabolism.
- Many disease state like cirhosis affect metabolism.
- Hormonal imbalance may inhibit or induce the enzyme activities.

Stereochemical Aspects of Drug Metabolism

some microsomal enzyme systems show preference towards one enantiomer of a drug over the other. This is called enantioselectivity.