



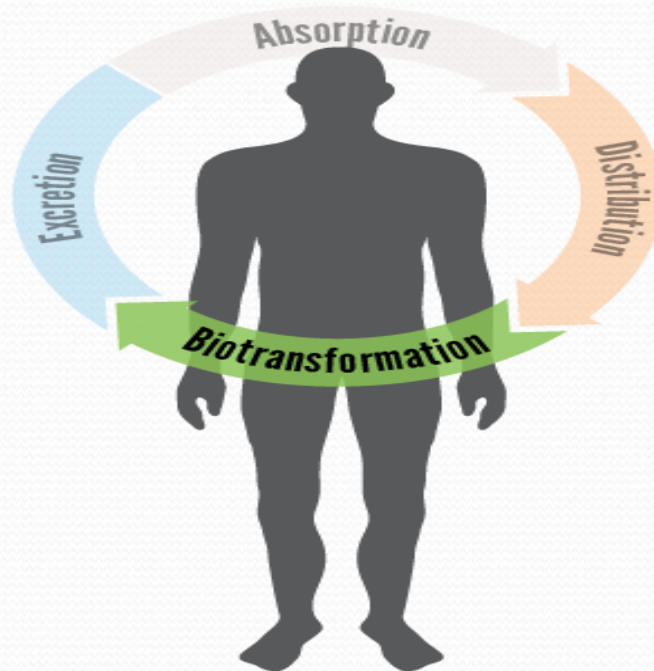
**Biopharmaceutics & Pharmacokinetics**  
**8<sup>th</sup> SEM**

**Biotransformation of  
drug - Phase I  
reactions**

**Dr. Praveen Khirwadkar**  
**Institute of Pharmacy**  
**Vikarm University**  
**Ujjain**

# INTRODUCTION

- Biotransformation is a chemical alteration of the drug in body that converts non-polar or lipid soluble compounds to polar or lipid insoluble compounds so that they are not reabsorbed but eliminated



```
graph TD; A[Biotransformation] --> B[Bioactivation]; A --> C[Bioinactivation];
```

**BIOTRANSFORMATION**

**BIOACTIVATION**

**BIOINACTIVATION**

# SIGNIFICANCE OF BIOTRANSFORMATION

- conversion of an active drug to inactive or less active metabolites called as pharmacological inactivation.
- conversion of an active to more active metabolite called as bioactivation or toxicological activation.
- conversion of an inactive to more active toxic metabolite called as lethal synthesis
- conversion of an inactive drug (pro-drug) to active metabolite called as pharmacological activation
- conversion of an active drug to equally active metabolite (no change in pharmacological activity)
- conversion of an active drug to active metabolite having entirely different pharmacological activity (change in pharmacological activity)

# SITE OF BIOTRANSFORMATION

- The major site of drug metabolism is the liver (microsomal enzyme systems of hepatocytes)
- Secondary organs of biotransformation
  - kidney (proximal tubule)
  - lungs (type II cells)
  - testes (Sertoli cells) skin (epithelial cells)
  - plasma.
  - nervous tissue (brain); intestines

- Metabolism by organs other than liver (called as extra-hepatic metabolism) is of lesser importance because lower level of metabolising enzymes is present in such tissues.
- Within a given cell, most drug metabolising activity is found in the smooth endoplasmic reticulum and the cytosol
- Drug metabolism can also occur in mitochondria, nuclear envelope and plasma membrane.
- A few drugs are also metabolised by non-enzymatic means called as nonenzymatic metabolism.
- Eg; atracurium, a neuromuscular blocking drug, is inactivated in plasma by spontaneous non-enzymatic degradation (Hoffman elimination) in addition to that by pseudocholinesterase enzyme

<b>ORGANELLE</b>	<b>ENZYMES</b>
<b>ENDOPLASMIC RECTICULUM</b>	<p><b>PHASE 1:</b> cytochrome p450, FMO,aldehyde oxidase,carboxyesterase, epoxide hydrolase,prostaglandin synthase,esterase</p> <p><b>PHASE 2:</b> UDP glucuronosyltransferase, glutathione s-transferase,amino acid conjugating enzymes</p>
<b>CYTOSOL</b>	<p><b>PHASE 1:</b>alcohol dehydrogenase, aldehyde reductase,aldehyde dehydrogenase,epoxide hydrolase,esterase</p> <p><b>PHASE 2:</b>sulfotransferase, glutathione s-transferase,N-acetyl transferase,catechol-o-methyl transferase,aminoacid conjugating enzymes</p>
<b>MITOCHONDRIA</b>	<p><b>PHASE 1:</b>MAO,aldehyde dehydrogenase,cytochrome p450</p> <p><b>PHASE 2:</b>N-acetyl transferase,amino acid conjugating enzymes</p>
<b>LYSOSOME</b>	<b>PHASE 1:</b> peptidase
<b>NUCLEUS</b>	<b>PHASE 2:</b> UDP glucuronosyltransferase(nuclear membrane of enterocyte)

# Drug metabolising enzymes

ENZYMES	REACTIONS
<b>PHASE 1 “<i>Oxygenases</i>”</b> Cytochrome P450(CYP) Flavin containing monooxygenase(FMO) Epoxide hydrolases(Meh,sEH)	C & O oxidation,dealkylation N,S & P oxidation Hydrolysis of epoxides
<b>PHASE 2 “<i>Transferases</i>”</b> Sulfotransferases(SULT) UDP-glucuronosyltransferases(UGT) Gluthionine S-transferases(GST) N-acetyltransferases(NAT) Methyltransferases(MT)	Addition of sulfate Addition of glucuronic acid Addition of glutathione Addition of acetyl group Addition of methyl group
<b>OTHER ENZYMES</b> Alcohol dehydrogenase Aldehyde dehydrogenase NADPH-quinone oxidoreductase(NQO)	Reduction of alcohols Reduction of aldehydes Reduction of quinones



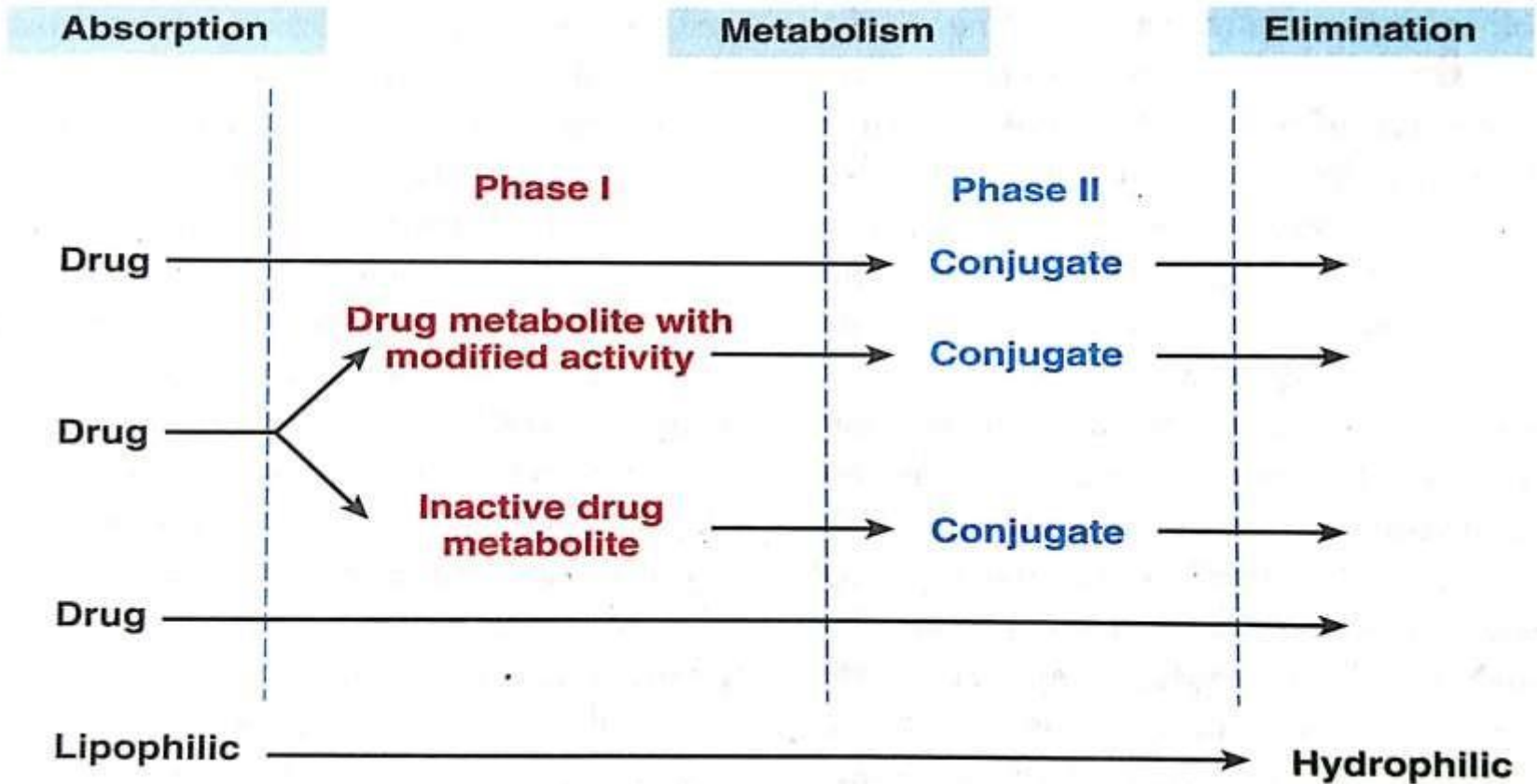
# Drug metabolising enzymes

Drug metabolising enzymes can be broadly divided into two

- groups:
- Microsomal Non-microsomal

MICROSOMAL	NON MICROSOMAL
Found on ER	Found on sites other than ER, usually present in the cytoplasm, mitochondria etc
Catalyse glucuronide conjugation, most oxidative reactions, and some reductive and hydrolytic reactions	Non specific enzymes that catalyse few oxidative, reductive, all conjugative reactions other than glucuronidation
Eg; cytochrome p450 monooxygenase, flavin mono oxygenase	Eg: alcohol dehydrogenase, aldehyde dehydrogenase, mono & diamine oxidase

# PHASES OF BIOTRANSFORMATION



# Thank You

