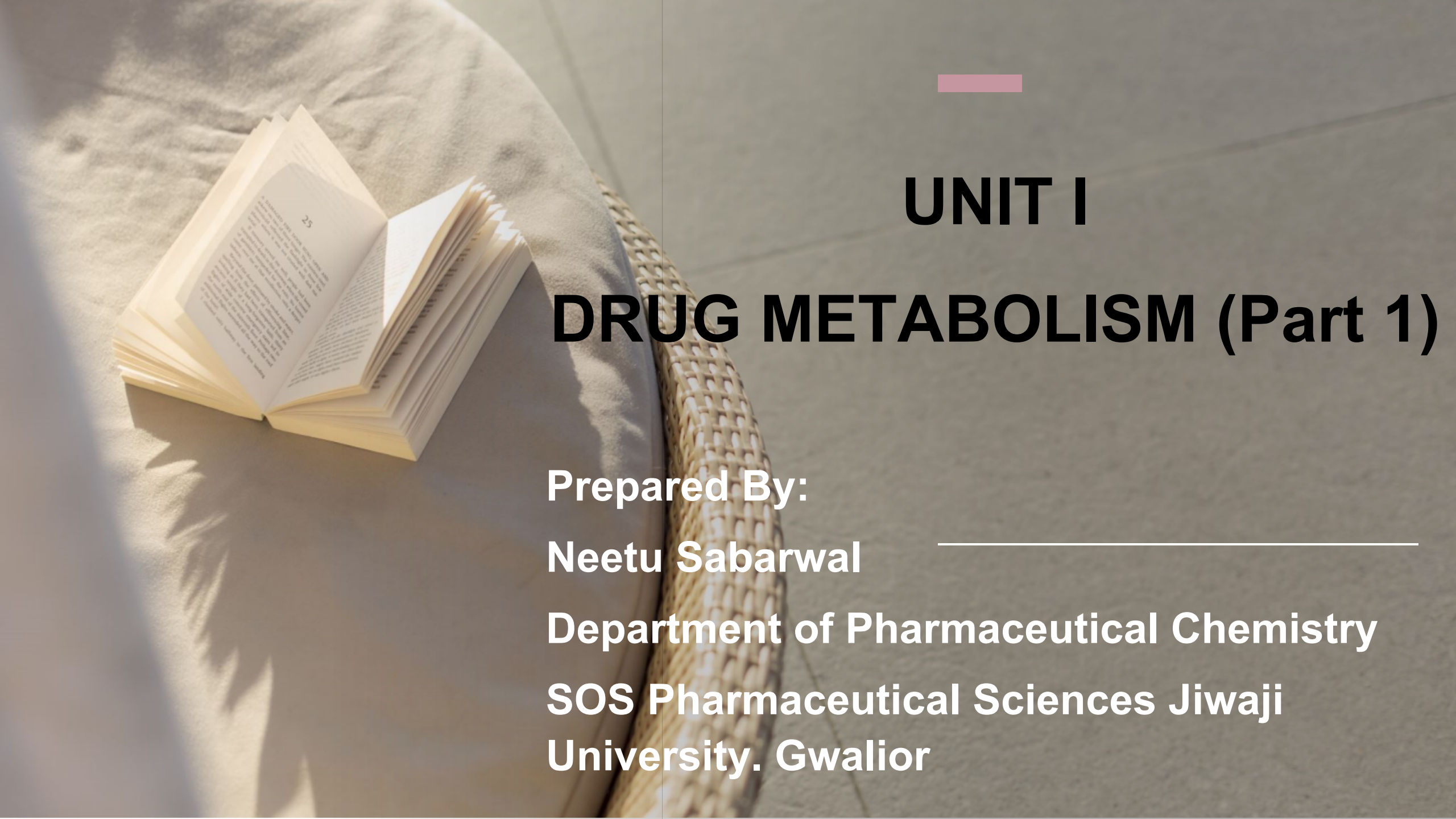

UNIT I

DRUG METABOLISM (Part 1)

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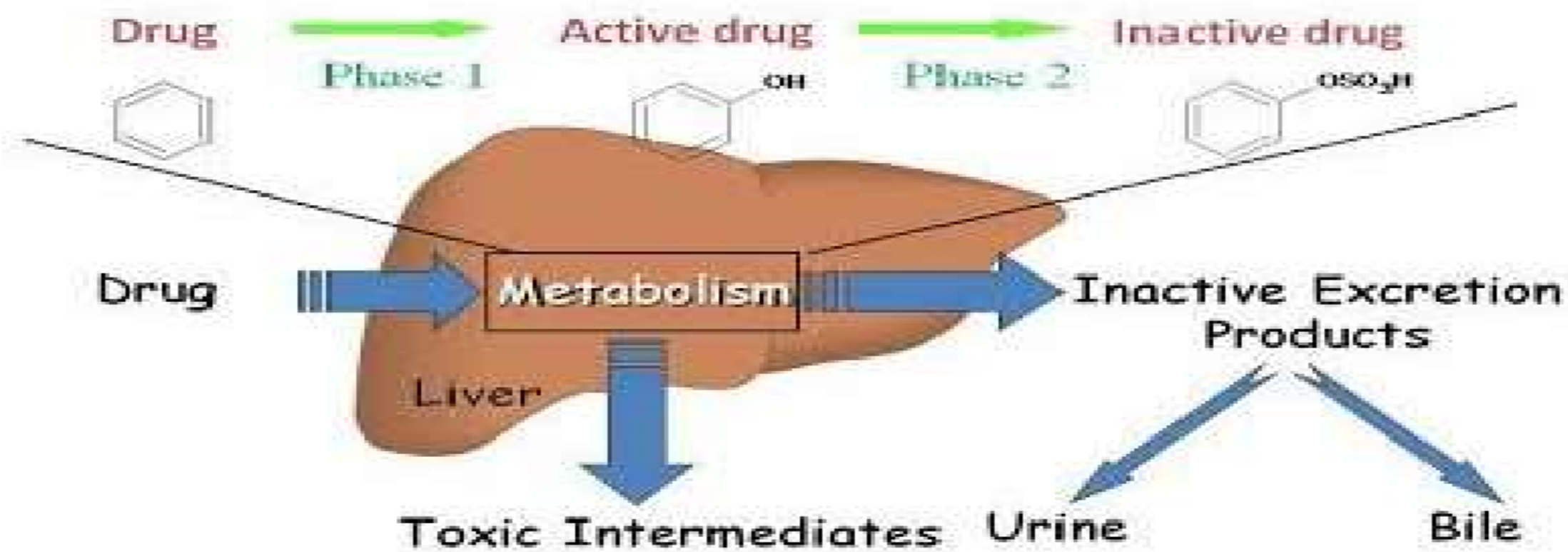
DRUG METABOLISM



DRUG METABOLISM

- **Definition:** Process of converting a drug into product or inert substances after or before reaching at the site of action.
- **Metabolism** is an essential pharmacokinetic process, which render lipid soluble and non polar compounds to water soluble and polar compounds so that they are excreted by various process from the body.
- **Biotransformation:** It is a specific term used for the chemical transformation of xenobiotics in the living organisms.
- **Xenobiotics**: These are all chemical substances that are not nutrient for the body (foreign body) and which enter the body through ingestion, inhalation or dermal exposure.

DRUG METABOLISM

- Most organic compounds entering the body are relatively lipid soluble (lipophilic).
- To be absorbed, they must traverse the lipoprotein membranes of the lumen walls of the gastrointestinal (GI) tract.
- Then, once in the bloodstream, these molecules can diffuse passively through other membranes and be distributed effectively to reach various target organs to exert their pharmacological actions.
- Because of reabsorption in the renal tubules, lipophilic compounds are not excreted to any substantial extent in the urine.

DRUG METABOLISM

- Xenobiotics then meet their metabolic fate through various enzyme systems that change the parent compound to render it more water soluble (hydrophilic).
- Once the metabolite is sufficiently water soluble, it may be excreted from the body.
- The previous statements show that a working knowledge of the ADME (absorption, distribution, metabolism, and excretion) principles is vital for successful determination of drug regimens.

DRUG METABOLISM

- If lipophilic drugs, or xenobiotics, were not metabolized to polar, readily excretable water-soluble products, they would remain indefinitely in the body, eliciting their biological effects.
- Thus, the formation of water-soluble metabolites not only enhances drug elimination, but also leads to compounds that are generally pharmacologically inactive and relatively nontoxic.

DRUG METABOLISM

- Consequently, drug metabolism reactions have traditionally been regarded as detoxication (or detoxification) processes.
- Unfortunately, it is incorrect to assume that drug metabolism reactions are always detoxifying.
- Many drugs are biotransformed to pharmacologically active metabolites. These metabolites may have significant activity that contributes substantially to the pharmacological or toxicological effects ascribed to the parent drug.
- Occasionally, the parent compound is inactive when administered and must be metabolically converted to a biologically active drug (metabolite).
- These types of compounds are referred to as **Prodrugs**.

Functions of Biotransformation

❖It causes conversion of an active drug to inactive or less active metabolite(s) called as **pharmacological inactivation**.

Phenobarbitone	p-Hydroxyphenobarbitone
Phenytoin	p-Hydroxyphenytoin
Procaine	p-Aminobenzoic acid
Griseofulvin	6-Demethylgriseofulvin

❖It causes conversion of an active to more active metabolite(s) called as **bioactivation** or **toxicological activation.**

Codeine	Morphine
Paracetamol	Imidoquinone of N-hydroxylate metabolite
Sulphonamides	Acetyl derivatives
Malathion	Malaoxon
Halothane	Trifluoroacetic acid

- It causes conversion of an inactive to more active toxic metabolite(s) called as **lethal synthesis**

Functions of Biotransformation....contd

- It causes conversion of an inactive drug (pro-drug) to active metabolite(s) called as **pharmacological activation**

Phenacetin	Paracetamol
Enalapril	Enalaprilat
Pivampicillin	Ampicillin
Sulphasalazine	5-Aminosalicylic acid
Levodopa	Dopamine

- It causes conversion of an active drug to equally active metabolite(s) (**no change** in pharmacological activity)

Digitoxin	Digoxin
Diazepam	Nordiazepam
Amitriptyline	Nortriptyline
Phenylbutazone	Oxyphenbutazone

- It causes conversion of an active drug to active metabolite(s) having entirely different pharmacological activity (**change** in pharmacological activity)

Iproniazid (antidepressant)	Isoniazid (antitubercular)

Sites of Metabolism

- Liver
- GIT
- Lungs
- Kidney
- Plasma
- Skin
- Nasal Mucosa
- Others

Site/Organs of drug metabolism

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

Sites of Biotransformation...contd

Liver

- The primary site for metabolism of almost all drugs because it is relatively rich in a large variety of metabolising enzymes.

- 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 cytoso**l.
- Drug metabolism can also occur in mitochondria, nuclear envelope and plasma membrane.

- A few drugs are also metabolised by non-enzymatic means called as non-enzymatic metabolism.

- **Microsomal enzymes**: The endoplasmic reticulum (especially smooth endoplasmic reticulum) of liver and other tissues contain a large variety of enzymes, together called microsomal enzymes

- (microsomes are minute spherical vesicles derived from endoplasmic reticulum after disruption of cells by centrifugation, enzymes present in microsomes are called microsomal enzymes).

- They catalyse glucuronide conjugation, most oxidative reactions, and some reductive and hydrolytic reactions.

- The monooxygenases, glucuronyl transferase, etc are important microsomal enzymes.

- **Non-microsomal enzymes**: Enzymes occurring in organelles/sites other than endoplasmic reticulum (microsomes) are called non-microsomal enzymes.

- These are usually present in the cytoplasm, mitochondria, etc. and occur mainly in the liver, GI tract, plasma and other tissues.

- They are usually non-specific enzymes that catalyse few oxidative reactions, a number of reductive and hydrolytic reactions, and all conjugative reactions other than glucuronidation.

- None of the non-microsomal enzymes involved in drug biotransformation is known to be inducible.

TYPES

BIOTRANSFORMATION REACTIONS - 2 TYPES

- **Phase I / Non synthetic / Functionalization**
  - A functional group is generated
  - Metabolite – active or inactive

- **Phase II / Synthetic / Conjugation**
- An endogenous radical is conjugated
- Metabolite is usually inactive

TYPES OF BIOTRANSFORMATION

Phase 1 reaction. (Non synthetic phase).

- a change in drug molecule. generally results in the introduction of a functional group into molecules or the exposure of new functional groups of molecules

❖ : Phase I (non-synthetic or non-conjugative phase) includes reactions which catalyse **oxidation, reduction and hydrolysis of drugs.**

❖ In phase I reactions, small polar functional groups like-OH, -NH_2. -SH, -COOH, etc. are either added or unmasked (if already present) on the lipid soluble drugs so that the resulting products may undergo phase II reactions.

- result in **activation, change or inactivation of drug.**

Phase II reaction. (Synthetic phase)

- Last step in detoxification reactions and almost **always results in loss of biological activity of a compound**.
- May be preceded by one or more of phase one reaction
- Involves conjugation of functional groups of molecules with hydrophilic endogenous substrates- **formation of conjugates -** is formed with (an endogenous substance such as carbohydrates and amino acids.)with drug or its metabolites formed in phase 1 reaction.

❖ Involve attachment of small polar endogenous molecules like glucuronic acid, sulphate, methyl, amino acids, etc., to either unchanged drugs or phase I products.

❖ **Products called as 'conjugates' are water-soluble metabolites**, which are readily excreted from the body.

- **Phase I metabolism is sometimes called a "functionalization reaction,"**
- Results in the introduction of new hydrophilic functional groups to compounds.
- **Function:** introduction (or unveiling) of functional group(s) such as –OH, –NH2, –SH, –COOH into the compounds.
- **Reaction types:** oxidation, reduction, and hydrolysis

- **Enzymes:**
- *Oxygenases and oxidases:* Cytochrome P450 (P450 or CYP), flavincontaining
- monooxygenase (FMO), peroxidase, monoamine oxidase(MAO), alcohol dehydrogenase, aldehyde dehydrogenase, and xanthine 0xidase. *Reductase:* Aldo-keto reductase and quinone reductase.
- *Hydrolytic enzymes*: esterase, amidase, aldehyde oxidase, and alkylhydrazine
- oxidase.
- Enzymes that scavenge reduced oxygen: Superoxide dismutases, catalase,
- glutathione peroxidase, epoxide hydrolase, *y-glutamyl transferase,*
- dipeptidase, and cysteine conjugate β-lyase

- **Phase II metabolism includes what are known as conjugation reactions.**
- Generally, the conjugation reaction with endogenous substrates occurs on the metabolite(s) of the parent compound after phase I metabolism; however, in some cases, the parent compound itself can be subject to phase II metabolism.
- **Function:** conjugation (or derivatization) of functional groups of a compound or its metabolite(s) with endogenous substrates.
- **Reaction types**: glucuronidation, sulfation, glutathione-conjugation, Nacetylation, methylation and conjugation with amino acids (e.g., glycine, taurine, glutamic acid).
- **Enzymes:** Uridine diphosphate-Glucuronosyltransferase (UDPGT): sulfotransferase (ST), N-acetyltransferase, glutathione S-transferase (GST),methyl transferase, and amino acid conjugating enzymes.
- Glucuronidation by uridine diphosphate-glucuronosyltransferase; Sulfation by sulfotransferase
- 3. Acetylation by N-acetyltransferase; Glutathione conjugation by glutathione S-transferase;. Methylation by methyl transferase; Amino acid conjugation

DRUG METABOLISM

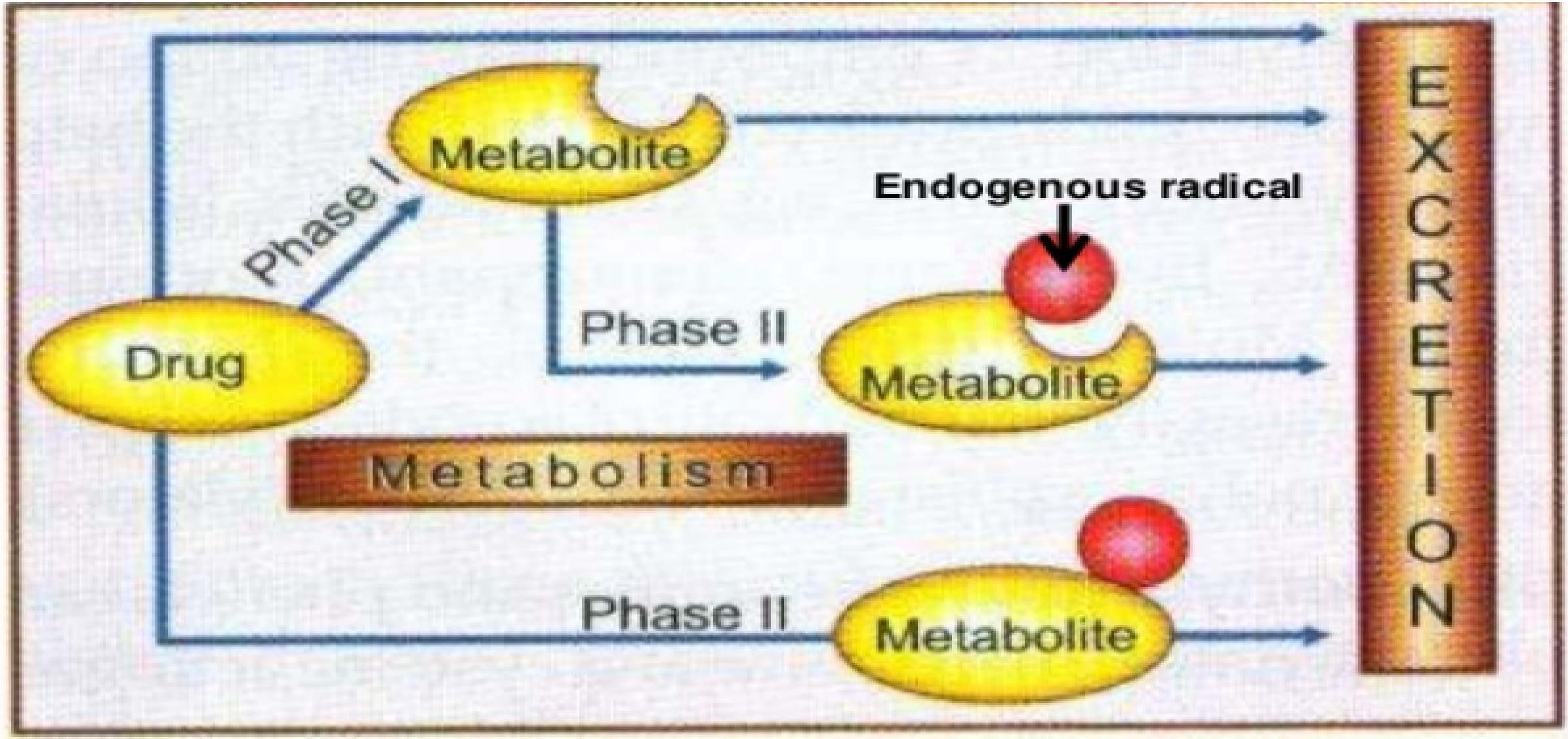


Fig. 3.1: Simultaneous and/or sequential metabolism of a drug by phase I and phase II reactions

The detailed discussion about Phase I and Phase II reactions will proceed in the next part of slides

THANK YOU