INTRODUCTION

The average day-to-day humans are exposed to various forms of chemicals whether it is through the consumption of food or water, exposure to air pollutants and most often during drug utilisation. The physiology of the human body has a unique mechanism to eliminate these extraneous compounds and ultimately sustain the body’s homeostasis to prevent further illnesses. This process occurs within the liver following the absorption of drugs and nutrients across the small intestines. The human liver produces a cascade of enzymes that are collectively responsible for converting lipid-soluble compounds (lipophilic) into a more water-soluble substance (hydrophilic) to facilitate their elimination from the body by urination or defecation [1].

THE MECHANISMS OF DRUG METABOLISM

The process of drug metabolism may be defined as the biochemical modification of pharmaceutical agents by different enzymatic pathways to prepare the substance for elimination from the body [3]. Drug metabolism consists of two classes of reactions, known as Phase I and Phase II. Both phases are unique and vary by their processes of chemical modification, whereas Phase I breaks down metabolites (catabolic) and Phase II formulates substances (anabolic) by the attachment of a substituent group [2]. Ultimately, both reactions decrease the occurrence of lipid-soluble compounds and generate species of polar molecules, which are hydrophilic and more susceptible to excretion via the renal pathway [1, 2]. The nature of the drug determines whether it will undergo Phase I or II modification and in some cases, the drug will be biotransformed by both phases [2].

IN THE LIVER – PHASE I & II

Phase I:
- Occurs in the smooth endoplasmic reticulum (SER) of the liver cells [2].
- Contains hepatic drug-metabolising enzymes (Cytochrome P450) referred to as CYP [1, 2].

Phase II:
- Occurs in the cytosolic fraction of the liver cells [4, 6].
- Contains non-microsomal enzymes and cofactors.
PHASE I

The initial stage of the drug metabolic process is a catabolic reaction consisting of different oxidase systems responsible for the oxidation, reduction or hydrolysis of a drug molecule \[1\]. A distinguishable characteristic of Phase I is its occurrence in the SER of the liver cell, which contains the membrane-bound enzyme CYP that catalyses the catabolic reaction in Phase I \[2\]. The microsomal enzyme composes of a haemoprotein that is responsible for the oxidation of the lipophilic compound into a more polar metabolite for excretion \[3\]. The enzymatic reaction interacts with the drug molecule by one of three oxidase systems:

- **Oxidation**: The most frequent reaction that occurs in the Phase I metabolism. Responsible for increasing the hydrophilicity of the target molecule through the addition of a polar functional group such as hydroxyl (oxygen bonded to hydrogen) \[1, 2\].
- **Reduction**: A reaction that generates a polar functional group through the removal of an oxygen molecule within the drug molecule \[1, 6\].
- **Hydrolysis**: A process in which non-microsomal enzymes convert esters and amides into carboxylic acids and alcohols, which are water soluble substances that can be excreted through renal processing \[1, 4, 6\].

The final product of Phase I metabolism may possess two different results. First case, the drug metabolite is pharmacologically inactive and is eliminated from the body by transportation to the kidneys or carried to Phase II for further biotransformation \[7\]. Second case, the metabolite is still pharmacologically active but less so than the original substance (prodrug) \[7, 8\]. The general danger of Phase I metabolism is the potential biotransformation of a nontoxic compound into a toxic metabolite, which results in hepatotoxicity (liver-induced toxicity) \[9, 10\].

EXAMPLE: PHASE I – ACETAMINOPHEN (PARACETAMOL)

Acetaminophen (APAP), also known as paracetamol is a conventional analgesic used to relieve mild to moderate pain. The potential for hepatotoxicity is considered during significant ingestion of APAP (approximately 13g for a 75kg human) \[10\]. In Phase I metabolism, the hepatic enzyme CYP converts APAP into the reactive metabolite \textit{N}-acetyl-p-benzoquinone imine (NAPQI) \[9\]. The production of NAPQI induces oxidative stress within the liver cells which corresponds to necrotic cell death and eventual liver failure \[9, 10\].
PHASE II

The second stage of metabolism is an anabolic reaction that consists of conjugating enzymes responsible for increasing the water solubility of substrates by the addition of a polar substituent \[1\]. The activity of phase II metabolism occurs within the cytosolic region of the liver cells, containing a collection of enzymes and cofactors that conjugates the earlier oxidised product from stage one. The process of conjugation involves the addition of a hydrophilic group to the drug molecule, thereby inactivating its pharmacological activity and increasing its ability to bind to water within the kidneys for excretion. The class of conjugate that is attached to the drug molecule ranges from \([1, 2, 5]\):

- Glucuronidation, the addition of glucuronic acid that is catalysed by the enzyme UGT.
- Sulfation, the addition of a sulfate group that is catalysed by the enzyme SULTs.
- Glutathione conjugation is the addition of glutathione to prevent damage by reactive oxygen species.
- Acetylation, the addition of an acetate group that is catalysed by the enzyme N-Acetyl transferase.

A significant difference of Phase II metabolism from Phase I is the complete inactivation of the parent drug’s pharmacological activity.

EXAMPLE: PHASE II – CHLORAMPHENICOL

Chloramphenicol is an antibiotic prescribed for the treatment of bacterial infections occurring in the eyes. The prodrug undergoes Phase II metabolism by the process of Glucuronidation, the addition of a conjugate group known as glucuronic acid that is catalysed by the enzyme UGT. The chemical properties of the drug contain two hydroxyl groups which allow the conjugate group to bind to thereby, inactivating the drug’s therapeutic effects. The drug metabolite, chloramphenicol glucuronide is inactivated and ready for transportation to the kidneys for urinary excretion.
REFERENCES


