D. PHARMACY

(II YEAR)

PHARMACOLOGY – THEORY

Course Code: ER20-21T

UNIT -1
Chapter: 1 General Pharmacology

INTRODUCTION AND SCOPE OF PHARMACOLOGY

Pharmacology is the branch of science that studies drugs and their effects on living organisms. It is concerned with understanding the interactions between chemicals and biological systems, focusing on how drugs influence the functioning of the body.

Core Areas of Pharmacology

1. **Pharmacodynamics**: Focuses on the effects of drugs on biological systems and how they produce their therapeutic or toxic effects. This includes studying mechanisms of action, receptor interactions, and dose-response relationships.
2. **Pharmacokinetics**: Examines how the body affects the drug, including processes of absorption, distribution, metabolism, and excretion (ADME). It helps understand drug concentration in the bloodstream and tissues over time.
3. **Toxicology**: Deals with the adverse effects of chemicals on living organisms, determining the safety and potential harm of drugs and chemicals.
4. **Clinical Pharmacology**: The application of pharmacological principles in the real-world setting of patient care. It focuses on optimizing drug therapy for individuals, considering the efficacy and safety of treatments.
5. **Neuropharmacology**: Specializes in the effects of drugs on the nervous system and behavior.
6. **Psychopharmacology**: Deals with drugs that affect mood, behavior, and cognition, including treatments for psychiatric disorders.

Scope of Pharmacology

Pharmacology is a vast field with multiple sub-disciplines, each focusing on different aspects of drugs and their effects. Some of the major areas of pharmacology include:

1. **Clinical Pharmacology**:
    - Focuses on the therapeutic use of drugs in humans.
    - Studies how drugs can be used to treat diseases and how to optimize drug dosages.
    - Investigates drug interactions, side effects, and individual responses to medications.

2. **Neuropharmacology**:
    - Explores the effects of drugs on the nervous system.
    - Studies medications used to treat neurological disorders such as depression, anxiety, epilepsy, and Parkinson's disease.
3. **Cardiovascular Pharmacology**:
    - Examines how drugs affect the heart and blood vessels.
    - Involves studying treatments for hypertension, heart failure, and other cardiovascular diseases.
4. **Pharmacogenomics**:
    - Investigates how genetic variations affect individual responses to drugs.
    - Helps in the development of personalized medicine by tailoring drug therapy based on genetic profiles.
5. **Toxicology**:
    - Studies the harmful effects of chemicals and drugs.
    - Involves assessing the risk of exposure to various toxic substances, including environmental toxins.
6. **Chemotherapy**:
    - Involves the use of drugs to treat infections (antibiotics) and cancers (antineoplastic agents).
    - Focuses on designing drugs that can selectively target pathogens or cancer cells.
7. **Pharmacoeconomics**:
    - Evaluates the cost-effectiveness of drug therapies.
    - Studies the economic impact of drug treatments on healthcare systems.
8. **Development of New Drugs**:
    - Pharmacologists play a crucial role in drug discovery, testing, and development.
    - Involves preclinical studies, clinical trials, and post-marketing surveillance.

ROUTES OF DRUG ADMINISTRATION

It refers to the various pathways by which a drug can be delivered into the body. The choice of route depends on the drug's properties, the condition being treated, and patient factors. Each route has its advantages and disadvantages. Below are the major routes of drug administration:

1. Oral Route (Peroral, PO):

- **Definition**: Drugs are taken through the mouth and absorbed in the gastrointestinal (GI) tract.

Advantages:

- Convenient and non-invasive.
- Generally safer and painless.
- Easy for self-administration.

- Wide range of formulations (tablets, capsules, syrups).

Disadvantages:

- Slow onset of action (due to absorption through the GI tract).
- Subject to first-pass metabolism in the liver, which can reduce drug efficacy.
- Limited use in patients with nausea, vomiting, or unconsciousness.
- Some drugs may irritate the GI tract or have poor bioavailability when taken orally.

2. Intravenous (IV):

- **Definition**: Drug is directly injected into a vein, ensuring rapid delivery to the bloodstream.

Advantages:

- Rapid onset of action, ideal for emergencies.
- 100% bioavailability (no first-pass metabolism).
- Controlled drug delivery over time (infusions).
- Suitable for large volumes and irritant drugs that might harm tissues.

Disadvantages:

- Requires professional administration and sterile technique.
- Risk of infections or complications at the injection site.
- More invasive and uncomfortable.
- Higher risk of adverse reactions due to rapid delivery into the bloodstream.

3. Intramuscular (IM):

- **Definition**: Drug is injected into muscle tissue.

Advantages:

- Moderate onset of action.
- Suitable for depot injections (slow, sustained release over time).
- Easier to administer than IV.

Disadvantages:

- Can cause pain and tissue damage at the injection site.
- Limited to smaller volumes (up to 5 ml).
- Variability in absorption based on blood flow to the muscle.

4. Subcutaneous (SC):

- **Definition**: Drug is injected into the layer of fat beneath the skin.

Advantages:

- Slow, sustained absorption.
- Suitable for self-administration (e.g., insulin).
- Less painful than IM injections.

Disadvantages:

- Limited to small volumes (up to 2 ml).
- Slower onset than IM or IV.
- Risk of irritation or local tissue damage.

5. Sublingual (SL):

- **Definition**: Drug is placed under the tongue and absorbed through the mucous membranes.

Advantages:

- Rapid absorption into the bloodstream.
- Avoids first-pass metabolism.
- Convenient and easy to use.

Disadvantages:

- Limited to certain drugs that can be absorbed sublingually.
- Not suitable for large doses.
- May have an unpleasant taste or cause irritation in the mouth.

6. Rectal Route:

- **Definition**: Drug is administered via the rectum as a suppository or enema.

Advantages:

- Useful when oral administration is not possible (vomiting, unconsciousness).
- Reduced first-pass metabolism (partial).
- Suitable for both local and systemic effects.

Disadvantages:

- Absorption can be unpredictable.

- Discomfort or embarrassment for some patients.
- May cause local irritation.

7. Topical Route:

- **Definition**: Drug is applied directly to the skin or mucous membranes (e.g., creams, ointments, patches).

Advantages:

- Localized action with minimal systemic effects.
- Easy to apply and non-invasive.
- Some drugs (e.g., transdermal patches) provide sustained release.

Disadvantages:

- Limited to drugs that can be absorbed through the skin.
- Risk of skin irritation or allergic reactions.
- Slower absorption for systemic effects.

8. Inhalation Route:

- **Definition**: Drug is inhaled into the lungs, typically in aerosol or vapor form.

Advantages:

- Rapid onset due to large surface area and rich blood supply of the lungs.
- Direct delivery to the lungs for conditions like asthma.
- Avoids first-pass metabolism.

Disadvantages:

- Requires proper technique for optimal delivery (e.g., inhalers).
- Only suitable for drugs that can be formulated as aerosols or gases.
- Can cause local irritation in the respiratory tract.

9. Transdermal (Patch):

- **Definition**: Drug is delivered across the skin in a controlled-release system (patch).

Advantages:

- Sustained and controlled release over time.
- Convenient and non-invasive.
- Avoids first-pass metabolism.

Disadvantages:

- Slow onset of action.
- Limited to drugs that can penetrate the skin barrier.
- May cause skin irritation at the site of application.

10. Intrathecal:

- **Definition**: Drug is injected into the cerebrospinal fluid via the spinal cord.

Advantages:

- Direct delivery to the central nervous system (CNS), bypassing the blood-brain barrier.
- Useful for conditions like pain management or infections affecting the CNS.

Disadvantages:

- Invasive and requires skilled administration.
- Risk of infection, spinal injury, or complications.

11. Nasal Route:

- **Definition**: Drug is administered via the nasal mucosa, usually as a spray or drops.

Advantages:

- Rapid absorption through the nasal mucosa.
- Avoids first-pass metabolism.
- Suitable for both local and systemic effects.

Disadvantages:

- Limited to small doses.
- Nasal irritation or discomfort.
- Absorption may be inconsistent depending on nasal conditions (e.g., congestion).

Drug absorption - definition, types, factors affecting drug absorption

Drug absorption refers to the process by which a drug moves from its site of administration into the bloodstream. It is a crucial pharmacokinetic phase that determines the onset, intensity, and duration of a drug's effect. Absorption primarily occurs through membranes, depending on the route of administration, and can be influenced by various biological and chemical factors.

Types of Drug Absorption Mechanisms:

1. **Passive Diffusion**:
   - **Definition**: Drugs move across the cell membrane from an area of high concentration to an area of low concentration, without requiring energy.
   - **Characteristics**:
     - Most common absorption mechanism.
     - Lipid-soluble and non-ionized drugs are absorbed more easily.
     - No carrier required, and absorption rate depends on the concentration gradient and drug lipid solubility.
2. **Facilitated Diffusion**:
   - **Definition**: Drugs move across the membrane with the help of specific carrier proteins but still follow a concentration gradient (from high to low).
   - **Characteristics**:
     - No energy is required.
     - Used by drugs that cannot easily diffuse through the lipid bilayer (e.g., large, polar molecules).
3. **Active Transport**:
   - **Definition**: Drugs are transported across cell membranes against a concentration gradient (from low to high concentration) using energy (ATP).
   - **Characteristics**:
     - Requires specific carrier proteins.
     - Suitable for drugs resembling endogenous substances (e.g., vitamins, amino acids).
     - Can become saturated and is subject to competitive inhibition.
4. **Endocytosis and Exocytosis**:
   - **Definition**: Drugs are engulfed by the cell membrane (endocytosis) and brought into the cell, or they are expelled from the cell (exocytosis).
   - **Characteristics**:
     - Used for very large molecules (e.g., proteins, antibodies).
     - Endocytosis involves vesicle formation to transport the drug inside the cell.

Factors Affecting Drug Absorption

Several factors influence the rate and extent of drug absorption:

1. **Physicochemical Properties of the Drug**:
    - **Solubility**: Water-soluble drugs are absorbed better from aqueous environments, while lipid-soluble drugs are absorbed more readily through cell membranes.
    - **Molecular Size**: Smaller molecules are absorbed more quickly than larger ones.
    - **Ionization**: Non-ionized (uncharged) drugs are more easily absorbed, while ionized drugs may face barriers due to their charge. The degree of ionization depends on the drug's pKa and the pH of the environment.
    - **Formulation**: The physical form of the drug (e.g., tablets, solutions, suspensions) can affect how quickly the drug dissolves and is absorbed.
2. **Route of Administration**:
    - **Oral (Enteral)**: Drug absorption may be slow due to passage through the gastrointestinal (GI) tract, first-pass metabolism, and variable pH levels.
    - **Parenteral** (e.g., intravenous, subcutaneous, intramuscular): Absorption rates differ based on blood flow and the tissue type. IV administration bypasses absorption.
    - **Topical and Transdermal**: Absorption through the skin is generally slow but can be enhanced by patches for sustained release.
    - **Inhalation**: Provides rapid absorption due to the large surface area of the lungs.
3. **Blood Flow to the Absorption Site**:
    - Increased blood flow to the absorption site (e.g., muscles, lungs) enhances absorption.
    - Poor blood flow (e.g., in shock or dehydration) reduces absorption.
4. **Surface Area for Absorption**:
    - Larger surface areas, such as the small intestine or lungs, offer more opportunities for drug absorption compared to smaller or more restrictive areas.
5. **Gastrointestinal (GI) Factors**:
    - **Gastric Emptying and Motility**: Faster gastric emptying allows drugs to reach the small intestine more quickly, enhancing absorption.
    - **Presence of Food**: Food may either delay or enhance absorption, depending on the drug. Some drugs are best absorbed on an empty stomach, while others need food to reduce irritation.
    - **GI pH**: The pH of the stomach and intestines affects drug solubility and ionization. Acidic drugs are absorbed better in the stomach, while basic drugs are absorbed better in the intestines.
6. **Drug-Drug and Drug-Food Interactions**:
    - Other medications, supplements, or foods can interfere with drug absorption. For example, certain antibiotics may be poorly absorbed when taken with dairy products due to calcium binding.
7. **First-Pass Metabolism**:

- Drugs administered orally pass through the liver before entering the systemic circulation, and some may be extensively metabolized, reducing the amount that reaches the bloodstream. This can significantly affect drug bioavailability.

8. **Health Status and Physiological Factors**:
   - **Age**: Absorption may be slower in infants (due to immature GI systems) and the elderly (due to reduced blood flow and slower GI motility).
   - **Disease States**: Conditions like Crohn's disease, diarrhea, or reduced blood flow (due to cardiovascular issues) can reduce drug absorption.
   - **pH Alterations**: Medications like antacids can change the pH of the stomach, affecting drug solubility and absorption.

Bioavailability and the factors affecting bioavailability

Bioavailability refers to the proportion of an administered dose of a drug that reaches the systemic circulation in its active form and is available to produce a therapeutic effect. It is usually expressed as a percentage or fraction of the administered dose.

- **Absolute bioavailability** compares the bioavailability of a drug in systemic circulation after non-intravenous administration (oral, intramuscular, etc.) to the bioavailability after intravenous (IV) administration.
- **Relative bioavailability** compares the bioavailability of different formulations or routes of the same drug.

For instance, a drug administered intravenously has 100% bioavailability since it directly enters the bloodstream. However, for orally administered drugs, bioavailability is usually less than 100% due to factors like incomplete absorption and first-pass metabolism.

Factors Affecting Bioavailability

Several factors influence the extent and rate at which a drug becomes available in systemic circulation:

1. Physicochemical Properties of the Drug:

- **Solubility**: Drugs must dissolve in body fluids before absorption. Poorly soluble drugs often have lower bioavailability.
- **Stability**: Drugs that degrade in the acidic environment of the stomach or are susceptible to enzymes may have reduced bioavailability.
- **Molecular Size and Lipophilicity**: Small, lipophilic drugs can easily pass through cell membranes and typically have better bioavailability than large, hydrophilic drugs.
- **Ionization**: The ionization state of a drug affects its absorption. Non-ionized drugs can pass through membranes more easily, whereas ionized drugs may struggle.

2. Route of Administration:

- **Oral Route**: Often results in reduced bioavailability due to incomplete absorption and first-pass metabolism.
- **Intravenous Route**: Provides 100% bioavailability, as the drug directly enters the systemic circulation.
- **Transdermal, Inhalation, and Rectal Routes**: Can bypass or partially bypass first-pass metabolism and typically offer higher bioavailability than oral administration.

3. First-Pass Metabolism:

- **Definition**: After oral administration, drugs pass through the liver before reaching the systemic circulation. The liver metabolizes a portion of the drug, reducing the amount that reaches the bloodstream.
- Drugs that undergo extensive first-pass metabolism have significantly reduced bioavailability. For example, drugs like propranolol and nitroglycerin are heavily metabolized by the liver, resulting in low oral bioavailability.

4. Gastrointestinal (GI) Factors:

- **Gastric Emptying Time**: Faster gastric emptying allows drugs to move to the small intestine, where absorption is more efficient. Delayed gastric emptying can slow absorption and reduce bioavailability.
- **GI pH**: The pH in the stomach and intestines can influence drug solubility and ionization, affecting absorption. Acidic drugs (e.g., aspirin) are better absorbed in the stomach, while basic drugs (e.g., diazepam) are better absorbed in the intestine.
- **Intestinal Enzymes**: Enzymes in the GI tract may metabolize some drugs before absorption, reducing bioavailability.

5. Food and Diet:

- **Presence of Food**: Some drugs are best absorbed on an empty stomach, while others require food to enhance absorption or reduce side effects. Food can delay gastric emptying, change the pH of the GI tract, and interact with drug absorption (e.g., calcium-rich foods reducing absorption of tetracycline).
- **Dietary Composition**: High-fat meals can enhance the absorption of lipophilic drugs by stimulating bile secretion, while fiber-rich diets may decrease drug absorption by binding drugs in the intestine.

6. Drug Formulation Factors:

- **Dosage Form**: Different formulations (e.g., tablets, capsules, suspensions) dissolve and release drugs at varying rates, affecting absorption and bioavailability.
- **Excipients**: Inactive ingredients used in drug formulations (e.g., binders, fillers, coatings) can affect drug dissolution and absorption.
- **Controlled-Release Formulations**: Designed to release drugs slowly over time, resulting in sustained but potentially lower bioavailability compared to immediate-release forms.

7. Age and Health Conditions:

- **Age**: Infants and elderly individuals often have altered GI function and slower metabolism, which can affect drug absorption and bioavailability.
- **Liver and Kidney Function**: Impaired liver function reduces first-pass metabolism, potentially increasing bioavailability. Conversely, kidney disease can reduce drug clearance, affecting bioavailability.

- **Diseases of the GI Tract**: Conditions like Crohn's disease or malabsorption syndromes can impair drug absorption, leading to lower bioavailability.

8. Drug Interactions:

- **Drug-Drug Interactions**: Certain drugs can affect the absorption or metabolism of others. For example, drugs that alter GI motility (e.g., metoclopramide) can increase or decrease the absorption rate of other drugs.
- **Enzyme Induction and Inhibition**: Drugs that induce liver enzymes (e.g., rifampin) can enhance the metabolism of other drugs, reducing their bioavailability. Conversely, enzyme inhibitors (e.g., cimetidine) can reduce metabolism and increase bioavailability.

9. Transport Proteins and Efflux Pumps:

- **P-Glycoprotein (P-gp)**: This efflux pump, present in the intestinal lining, actively transports drugs back into the intestinal lumen, reducing their bioavailability. Drugs that are substrates of P-gp (e.g., digoxin) may have limited bioavailability due to this mechanism.

Drug distribution - definition, factors affecting drug distribution

Drug distribution refers to the process by which a drug is transported from the bloodstream to various tissues and organs after absorption or administration. Once in the systemic circulation, the drug spreads throughout the body, entering different compartments such as blood, tissues, extracellular fluids, and organs, where it may exert its therapeutic or toxic effects. The rate and extent of drug distribution depend on several physiological, physicochemical, and biochemical factors.

Factors Affecting Drug Distribution:

1. **Physicochemical Properties of the Drug**:
    - **Molecular Size**: Smaller molecules can diffuse more easily through biological membranes, allowing broader tissue distribution. Larger molecules may be restricted to certain compartments (e.g., blood plasma).
    - **Lipid Solubility**: Lipophilic (fat-soluble) drugs can readily cross cell membranes and are distributed widely, particularly to tissues with a high fat content (e.g., brain, adipose tissue). Hydrophilic (water-soluble) drugs tend to stay in the bloodstream or extracellular spaces.
    - **Degree of Ionization**: Ionized (charged) drugs are less likely to pass through cell membranes and tend to stay in the blood plasma or extracellular fluid, while non-ionized (uncharged) drugs can penetrate tissue barriers more easily.
2. **Blood Flow to Tissues**:
    - **Perfusion Rate**: Tissues and organs with higher blood flow (e.g., liver, kidneys, brain, heart) receive drugs more rapidly and extensively than areas with lower blood flow (e.g., fat, bone, skin). Drugs tend to distribute first to well-perfused organs and later to poorly perfused tissues.
    - **Regional Blood Flow**: Conditions that reduce blood flow (e.g., shock, hypotension) can impair drug distribution.
3. **Plasma Protein Binding**:
    - **Protein Binding**: Many drugs bind to plasma proteins such as albumin. Only the free (unbound) form of the drug is pharmacologically active and able to cross cell membranes. Highly protein-bound drugs are restricted in their distribution, as only the unbound fraction can leave the circulation and enter tissues.
    - **Competition for Binding**: Drugs can compete with each other for protein-binding sites. If two drugs are administered simultaneously and they both bind to the same protein, one drug may displace the other, increasing the concentration of the free drug in the plasma and enhancing its distribution and potential toxicity.
4. **Tissue Binding and Storage**:

- **Tissue Affinity**: Some drugs have a high affinity for specific tissues, leading to accumulation in those tissues. For example, certain drugs may bind to fat tissue (e.g., lipophilic drugs) or bone (e.g., tetracyclines), leading to prolonged storage and slow release over time.
- **Tissue Reservoirs**: Drugs stored in tissues or fat may act as reservoirs, releasing the drug slowly and prolonging its effects or delaying elimination.

5. **Permeability of Tissue Barriers**:
   - **Blood-Brain Barrier (BBB)**: The BBB is a specialized structure that limits the entry of many substances into the brain, protecting it from potential toxins. Only small, lipophilic, or transporter-mediated drugs can pass the BBB easily, limiting the distribution of many drugs to the central nervous system (CNS).
   - **Placental Barrier**: This barrier controls the transfer of drugs between the maternal and fetal blood. Lipophilic and non-ionized drugs can cross more easily, while polar and ionized drugs have restricted distribution across the placenta.
6. **Volume of Distribution (Vd)**:
   - **Definition**: Volume of distribution is a theoretical volume that relates the amount of drug in the body to the concentration of drug in the blood or plasma. A high Vd indicates that the drug is extensively distributed into tissues, while a low Vd suggests that the drug is confined to the bloodstream.
   - **Factors**: Drugs that are highly lipophilic or tissue-bound typically have a large Vd, whereas drugs that are highly protein-bound or water-soluble tend to have a small Vd.
7. **Lipid vs. Water Solubility**:
   - **Lipophilic Drugs**: Drugs that are fat-soluble distribute widely in tissues, particularly those with high fat content. For example, anesthetic drugs like thiopental rapidly accumulate in fatty tissues.
   - **Hydrophilic Drugs**: Water-soluble drugs primarily remain in the extracellular fluid and plasma. They have a lower volume of distribution and tend to be eliminated more rapidly.
8. **pH and Ion Trapping**:
   - **pH Differences**: The pH of various tissues and compartments affects drug ionization, which influences drug distribution. Ionized drugs cannot easily cross cell membranes, while non-ionized drugs can diffuse across membranes and distribute more easily.
   - **Ion Trapping**: If a drug becomes ionized in a tissue or compartment (based on the local pH and the drug's pKa), it may become "trapped" in that compartment. For example, weak acids tend to accumulate in basic compartments, and weak bases tend to accumulate in acidic compartments.

9. **Drug Transporters**:
    - **Efflux Transporters**: Certain transport proteins, such as P-glycoprotein (P-gp), can limit drug distribution by actively transporting drugs out of cells. These transporters are present in organs like the liver, intestines, and brain (e.g., the blood-brain barrier).
    - **Inhibition or Induction**: Drug transporters can be inhibited or induced by other drugs, which may affect the distribution of drugs that are substrates for these transporters.
10. **Physiological and Pathological Conditions**:

- **Age**: Infants and elderly individuals have different body compositions (e.g., higher water content in infants, lower water and more fat in the elderly), affecting drug distribution. Organ function, including liver and kidney function, also varies with age, altering distribution and metabolism.
- **Disease States**: Conditions like liver or kidney disease, obesity, and dehydration can affect blood flow, tissue perfusion, and plasma protein levels, leading to altered drug distribution.
- **Pregnancy**: Pregnancy alters blood volume, tissue composition, and protein binding, influencing drug distribution. Additionally, drugs can cross the placenta and distribute to the fetus.

Biotransformation

Biotransformation (also known as drug metabolism) refers to the chemical modification of a drug within the body, primarily by enzymatic processes, to convert the drug into a more water-soluble form that can be easily excreted. This process usually occurs in the liver, but other organs such as the kidneys, lungs, and intestines can also participate. The main goal of biotransformation is to detoxify and facilitate the elimination of drugs and xenobiotics from the body.

Biotransformation can result in:

- **Inactivation** of the drug.
- **Activation** of a prodrug (conversion to its active form).
- **Formation of active or toxic metabolites.**

Types of Biotransformation Reactions:

Biotransformation is categorized into two phases: **Phase I (Functionalization Reactions)** and **Phase II (Conjugation Reactions)**.

Phase I Reactions (Functionalization):

These reactions introduce or expose a functional group on the drug molecule (e.g., –OH, –NH2, –COOH), preparing it for further metabolism. Most Phase I reactions make drugs more polar, which aids in their elimination.

1. **Oxidation**:
    - **Enzymes**: Cytochrome P450 (CYP) enzymes, flavin-containing monooxygenases, alcohol dehydrogenase.
    - **Examples**:
        - Hydroxylation of aromatic and aliphatic groups.
        - N- and O-dealkylation.
        - Sulfoxidation (conversion of sulfur to sulfoxides).
        - Deamination (removal of an amine group).
    - **Significance**: Oxidation reactions are the most common Phase I reactions and usually lead to drug inactivation.
2. **Reduction**:
    - **Enzymes**: Reductases, including CYP reductases.
    - **Examples**:
        - Reduction of nitro compounds to amines.
        - Reduction of aldehydes to alcohols.

- **Significance**: These reactions are less common but can occur under anaerobic conditions (e.g., in the gut).

3. **Hydrolysis**:
   - **Enzymes**: Esterases, amidases.
   - **Examples**:
     - Hydrolysis of esters to alcohols and acids.
     - Hydrolysis of amides to amines and acids.
   - **Significance**: Hydrolysis reactions are important for breaking down ester and amide-containing drugs (e.g., local anesthetics, prodrugs).

Phase II Reactions (Conjugation):

These reactions involve the attachment of a polar group to the drug or its Phase I metabolite. This conjugation increases the water solubility of the drug, facilitating its excretion in urine or bile.

1. **Glucuronidation**:
   - **Enzyme**: UDP-glucuronosyltransferase (UGT).
   - **Substrate**: Hydroxyl, carboxyl, amine, or thiol groups.
   - **Example**: Glucuronidation of bilirubin, morphine, and acetaminophen.
   - **Significance**: This is the most common Phase II reaction, leading to the formation of highly water-soluble conjugates.
2. **Sulfation**:
   - **Enzyme**: Sulfotransferase.
   - **Substrate**: Hydroxyl and amine groups.
   - **Example**: Sulfation of steroid hormones, acetaminophen.
   - **Significance**: Sulfation often competes with glucuronidation and enhances drug excretion.
3. **Acetylation**:
   - **Enzyme**: N-acetyltransferase.
   - **Substrate**: Amines.
   - **Example**: Acetylation of isoniazid, sulfonamides.
   - **Significance**: Acetylation can reduce drug solubility, which in some cases (e.g., sulfonamides) may lead to crystalluria (crystals in urine).
4. **Glutathione Conjugation**:
   - **Enzyme**: Glutathione-S-transferase (GST).
   - **Substrate**: Electrophilic groups.
   - **Example**: Conjugation of reactive intermediates of drugs (e.g., toxic metabolites of acetaminophen).
   - **Significance**: This reaction is important for detoxifying reactive and toxic metabolites.

5. **Methylation**:
    - **Enzyme**: Methyltransferase.
    - **Substrate**: Catechols and phenols.
    - **Examples**: Methylation of catecholamines like dopamine and norepinephrine.
    - **Significance**: Methylation usually results in the inactivation of drugs or endogenous compounds.

Factors Influencing Drug Metabolism (Biotransformation):

Several factors affect how a drug is metabolized, leading to variations in drug efficacy, toxicity, and dosage requirements among individuals.

1. **Genetic Factors**:
    - **Genetic Polymorphisms**: Variations in genes encoding for drug-metabolizing enzymes (especially CYP450 enzymes) can lead to differences in metabolism rates. For example, individuals with different variants of the CYP2D6 gene may be classified as poor, intermediate, extensive, or ultra-rapid metabolizers.
    - **Enzyme Deficiencies**: Some individuals may lack specific enzymes (e.g., G6PD deficiency), affecting how they metabolize certain drugs.

2. **Age**:
    - **Neonates and Infants**: Infants have immature enzyme systems, leading to slower drug metabolism. This is particularly important for drugs that undergo glucuronidation (e.g., chloramphenicol).
    - **Elderly**: Metabolic activity decreases with age, often due to reduced liver function, affecting the clearance of drugs.
3. **Sex**:
    - Some drugs are metabolized differently in men and women due to hormonal differences, which can affect enzyme expression and activity.
4. **Liver Function**:
    - **Hepatic Diseases**: Liver diseases such as cirrhosis or hepatitis can impair the liver's ability to metabolize drugs, leading to higher drug levels in the blood and increased risk of toxicity.
5. **Nutritional Status**:
    - Malnutrition or deficiencies in essential nutrients (e.g., proteins, vitamins) can impair enzyme function and drug metabolism.

- **Co-factors**: Enzymes involved in drug metabolism require co-factors such as NADPH, which may be influenced by diet.

6. **Enzyme Induction and Inhibition**:
   - **Enzyme Induction**: Certain drugs (e.g., rifampin, phenobarbital) can increase the expression of metabolizing enzymes, speeding up the metabolism of other drugs. This can lead to reduced therapeutic efficacy.
   - **Enzyme Inhibition**: Some drugs (e.g., cimetidine, ketoconazole) inhibit metabolizing enzymes, slowing down drug metabolism and increasing the risk of toxicity.
7. **Drug-Drug Interactions**:
   - Concurrent administration of multiple drugs can lead to competition for the same metabolic pathways, resulting in altered drug levels and effects.
8. **Route of Administration**:
   - Drugs administered orally undergo **first-pass metabolism** in the liver, which can significantly reduce the amount of drug reaching systemic circulation. Other routes (e.g., intravenous, transdermal) may bypass or reduce first-pass effects.
9. **Environmental Factors**:
   - Exposure to environmental pollutants, smoking, and alcohol can induce certain enzymes, affecting drug metabolism.
10. **Diseases and Pathological Conditions**:
    - Diseases such as cardiovascular disorders, kidney dysfunction, and gastrointestinal conditions can affect drug metabolism by altering blood flow, enzyme function, or drug absorption.

Excretion of drugs - Definition, routes of drug excretion

Drug excretion is the process by which drugs and their metabolites are eliminated from the body. Once a drug has undergone metabolism (biotransformation), it must be excreted to terminate its pharmacological activity. Excretion typically involves the removal of water-soluble compounds, as lipid-soluble drugs are often reabsorbed unless they are metabolized into polar (water-soluble) metabolites. The primary organ involved in drug excretion is the kidney, but other organs such as the liver, lungs, and skin also contribute to the excretion process.

Routes of Drug Excretion:

1. **Renal Excretion (Kidneys)**:
    - **Primary route** for the excretion of most drugs and their metabolites, especially water-soluble compounds.
    - **Processes involved**:
        1. **Glomerular Filtration**: Drugs and metabolites are filtered from the blood into the urine. Only free (unbound) drugs can be filtered, as protein-bound drugs are too large to pass through the glomerulus.
        2. **Tubular Secretion**: Active transport systems in the proximal tubules can secrete drugs from the blood into the urine, including protein-bound drugs.
        3. **Tubular Reabsorption**: Lipid-soluble drugs may be reabsorbed back into the blood from the renal tubules, while polar, ionized drugs remain in the urine for excretion.
    - **Factors affecting renal excretion**: Urine pH, renal blood flow, kidney function.
    - **Examples**: Penicillin, digoxin, and many antibiotics are excreted through the kidneys.
2. **Hepatic Excretion (Bile)**:
    - **Biliary excretion** involves the secretion of drugs and metabolites into bile, which is then excreted into the intestines and eliminated in the feces.
    - **Drug characteristics**: Typically, large, polar molecules or those conjugated during metabolism (e.g., glucuronides) are excreted in bile.
    - **Enterohepatic circulation**: Some drugs excreted in bile can be reabsorbed into the bloodstream from the intestines, leading to prolonged drug action.
    - **Examples**: Drugs like steroids, some chemotherapeutic agents, and bile acid sequestrants.
3. **Pulmonary Excretion (Lungs)**:
    - Drugs that are volatile or gaseous (e.g., inhaled anesthetics, alcohol) can be excreted through the lungs by exhalation.

- **Examples**: Nitrous oxide, alcohol, and halothane.

4. **Gastrointestinal (GI) Excretion**:
   - Some drugs are directly excreted into the gastrointestinal tract and eliminated in the feces.
   - Drugs that are not absorbed after oral administration or are secreted into the intestines may be excreted via this route.
   - **Examples**: Oral contrast agents, non-absorbed antacids, and some antibiotics.
5. **Sweat and Saliva**:
   - A small fraction of drugs may be excreted through sweat and saliva, although this is not a significant route of excretion for most drugs.
   - **Significance**: Some drugs excreted in sweat may cause irritation, while those in saliva can lead to taste disturbances.
   - **Examples**: Lithium can be excreted through sweat and saliva.
6. **Breast Milk**:
   - Drugs can be excreted into breast milk and passed to a nursing infant, potentially leading to adverse effects in the child.
   - **Examples**: Antibiotics like tetracyclines, barbiturates, and certain antidepressants may be excreted into breast milk.
7. **Other Routes**:
   - **Tears**: Some drugs may be excreted into tears, leading to side effects such as eye irritation (e.g., rifampin can cause red tears).
   - **Hair**: Drugs can be deposited in hair, which is sometimes used in forensic testing to detect long-term drug use (e.g., for drugs like cocaine, opioids).

General Mechanisms of Drug Action

Drugs exert their effects in the body primarily by interacting with biological molecules, which alters the function of cells, tissues, or organs. These mechanisms can be divided into several broad categories:

1. **Receptor-mediated Drug Action**:
    - **Receptors** are specific proteins located on the surface or inside cells that drugs bind to, initiating a biological response. Receptors are often the primary targets for many drugs.
    - **Types of drug-receptor interactions**:
        - **Agonists**: Drugs that bind to receptors and activate them, mimicking the effect of endogenous substances (e.g., adrenaline acting on beta receptors).
        - **Antagonists**: Drugs that bind to receptors but do not activate them, blocking the action of agonists (e.g., beta-blockers blocking adrenaline).
        - **Partial agonists**: Drugs that bind and activate receptors but produce a weaker response than full agonists.
        - **Inverse agonists**: Drugs that bind to the same receptor as an agonist but produce the opposite effect (e.g., some antihistamines).
2. **Enzyme Inhibition**:
    - Some drugs act by inhibiting specific enzymes that are critical for certain biochemical reactions.
    - **Examples**:
        - **ACE inhibitors** (e.g., enalapril) inhibit angiotensin-converting enzyme, reducing blood pressure.
        - **Statins** inhibit HMG-CoA reductase, an enzyme involved in cholesterol synthesis, lowering cholesterol levels.
3. **Ion Channel Modulation**:
    - Drugs can alter the function of ion channels, which regulate the flow of ions across cell membranes, affecting the excitability of nerves and muscles.
    - **Examples**:
        - **Calcium channel blockers** (e.g., amlodipine) inhibit calcium ion entry into heart and vascular muscle cells, lowering blood pressure.
        - **Sodium channel blockers** (e.g., lidocaine) are used as local anesthetics by preventing nerve impulses.
4. **Transporter Proteins**:
    - Some drugs act by inhibiting transporter proteins responsible for moving molecules (e.g., neurotransmitters, ions) across cell membranes.
    - **Examples**:

        - **SSRIs** (e.g., fluoxetine) inhibit the serotonin transporter (SERT), increasing serotonin levels in the brain, which is used to treat depression.
        - **Diuretics** like furosemide act on ion transporters in the kidneys to increase urine output.
5. **Non-specific Drug Actions**:
    - Certain drugs produce effects without interacting with specific receptors or enzymes but rather through their physicochemical properties.
    - **Examples**:
        - **Osmotic diuretics** (e.g., mannitol) act by increasing the osmolarity of blood and renal filtrate.
        - **Antacids** neutralize stomach acid by a simple chemical reaction.
6. **Gene Modulation**:
    - Some drugs act by altering gene expression, leading to long-term changes in protein synthesis.
    - **Examples**:
        - **Corticosteroids** influence gene transcription by interacting with intracellular receptors that regulate the expression of anti-inflammatory proteins.

Factors Modifying Drug Action

Several factors can influence the pharmacological response to a drug, leading to variability in drug effects among different individuals. These include both patient-specific factors and drug-related factors.

1. **Age**:
    - **Neonates and infants**: Drug metabolism and excretion are immature in newborns, leading to prolonged drug effects. Drug dosing needs careful adjustment.
    - **Elderly**: Aging affects metabolism, renal function, and sensitivity to drugs, often requiring lower doses to avoid toxicity.
2. **Body Weight and Composition**:
    - Obesity or low body weight can influence the distribution and clearance of drugs. Lipid-soluble drugs may accumulate in fat tissues, altering their duration of action.
    - **Dosing by weight**: Some drugs require weight-based dosing to achieve the correct therapeutic effect.
3. **Genetic Factors**:

- **Pharmacogenetics** studies genetic differences in drug metabolism and response. Genetic polymorphisms in drug-metabolizing enzymes (e.g., CYP450 variants) can result in patients being classified as poor or rapid metabolizers, affecting drug efficacy and risk of toxicity.
- **Examples**: Variants in CYP2D6 affect the metabolism of codeine, resulting in poor analgesia or toxicity.

4. **Sex**:
   - Men and women may metabolize drugs differently due to hormonal differences, body composition, and genetic factors.
   - **Examples**: Women may have slower clearance of drugs like zolpidem (sleep aid) compared to men, increasing the risk of side effects.
5. **Route of Administration**:
   - The route of drug administration (oral, intravenous, intramuscular, etc.) affects the onset, intensity, and duration of drug action.
   - **Examples**: Drugs administered intravenously have a rapid onset, while oral drugs may be delayed by absorption processes and first-pass metabolism.
6. **Pathological Conditions**:
   - **Liver disease**: Impaired liver function affects drug metabolism, leading to increased drug levels and risk of toxicity.
   - **Kidney disease**: Renal impairment slows drug excretion, requiring dose adjustments to avoid accumulation.
   - **Heart failure**: Reduces blood flow to organs, affecting drug distribution and clearance.
7. **Tolerance and Tachyphylaxis**:
   - **Tolerance**: Decreased response to a drug after repeated use, often requiring higher doses to achieve the same effect. This can develop with drugs like opioids and benzodiazepines.
   - **Tachyphylaxis**: Rapid reduction in drug response after a few doses, often seen with drugs like nitrates.
8. **Drug-Drug Interactions**:
   - Concurrent use of multiple drugs can lead to interactions, affecting absorption, metabolism, or excretion. Drugs may either enhance or inhibit the action of another.
   - **Examples**:
     - Enzyme inducers (e.g., rifampin) increase the metabolism of other drugs, reducing their efficacy.
     - Enzyme inhibitors (e.g., ketoconazole) slow drug metabolism, increasing the risk of toxicity.
9. **Diet and Nutritional Status**:

- Certain foods can affect drug metabolism (e.g., grapefruit juice inhibits CYP3A4 enzymes), while malnutrition or vitamin deficiencies can alter drug response.
- **Protein binding**: In malnourished individuals, lower levels of plasma proteins can result in more free drug in circulation, increasing the risk of toxicity.

10. **Psychological Factors**:
    - The placebo effect can influence drug action, where patients experience improvements based on their belief in the treatment, even if the drug has no therapeutic effect.