PHARMACOKINETICS (DRUG DISTRIBUTION AND METABOLISM)

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Pharmacology, MA 411

Spring Semester

4th week

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Outline

- Drug distribution
- Drug metabolism

Objectives

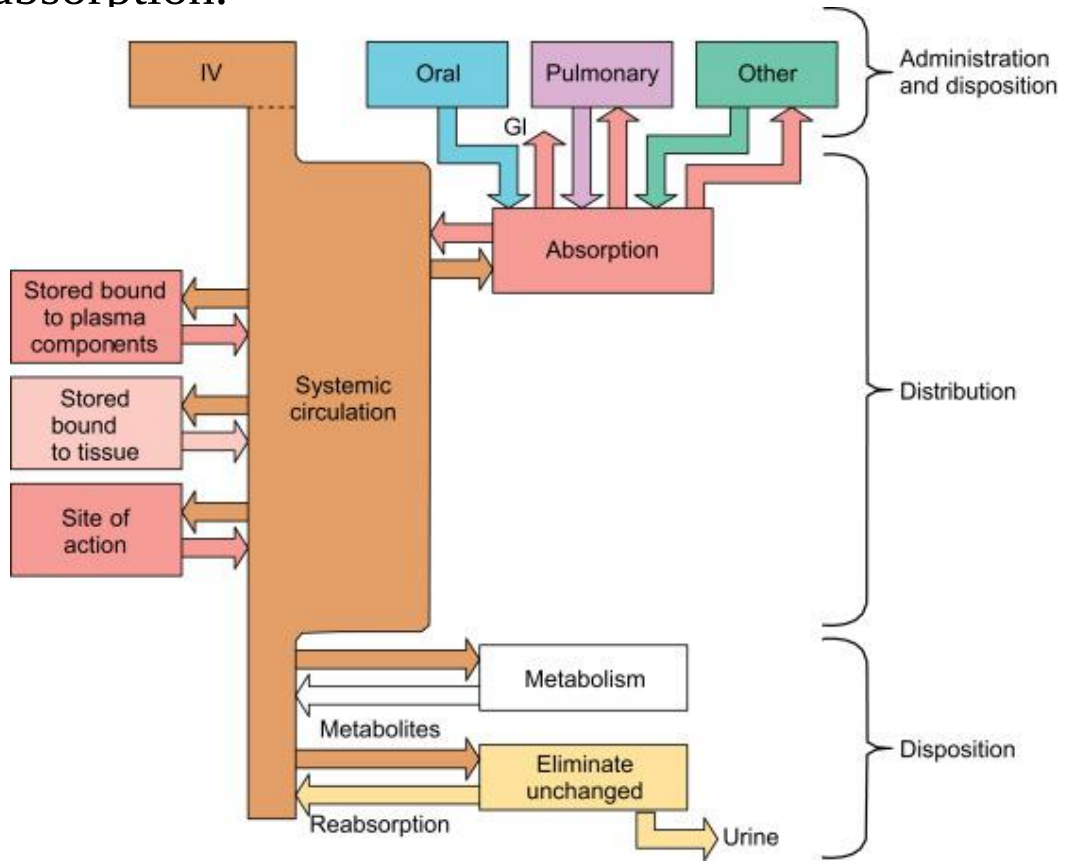
At the end of the lesson, the students should be able to understand:

1. Describe drug distribution
2. Learn about factors affecting drug distribution
3. Being familiar with volume of distribution (Vd).
4. Accumulation of drugs in peripheral compartments.
5. Describe drug metabolism
6. Learn about phases of drug metabolism
7. Site of drug metabolism
8. Factors affecting drug metabolism

Drug distribution

- **Drug distribution** is a crucial phase of pharmacokinetics, which describes how a drug moves from the bloodstream into various tissues and organs after absorption.

- After a drug enters the systemic circulation, it is distributed to the body's tissues.



Factors affecting drug distribution

1. Blood flow to tissues

Highly perfused organs (brain, liver, kidneys) receive drugs rapidly. However, poorly perfused tissues (fat, bone, and skin) receive drugs more slowly.

2. Plasma protein binding

Many drugs bind to plasma proteins such as albumin and globulins. Free (unbound) drug is pharmacologically active and can cross membranes. Highly protein-bound drugs may have a longer duration of action.

Factors affecting drug distribution

3. Lipid solubility

Lipophilic (fat-soluble) drugs easily cross cell membranes and accumulate in tissues. However, hydrophilic (water-soluble) drugs remain mostly in the extracellular fluid.

4. Capillary permeability

The structure of capillary walls affects drug movement. The blood-brain barrier and placental barrier restrict drug penetration due to tight junctions.

Volume of distribution (Vd)

Volume of distribution (Vd) is a theoretical parameter that describes the extent to which a drug is distributed throughout body tissues relative to the plasma concentration.

$\boldsymbol{Vd}$ = Amount of drug in the body (Dose) / Plasma drug concentration (C)

High Vd (>40 L) → The drug extensively distributes into tissues (e.g., lipophilic drugs).

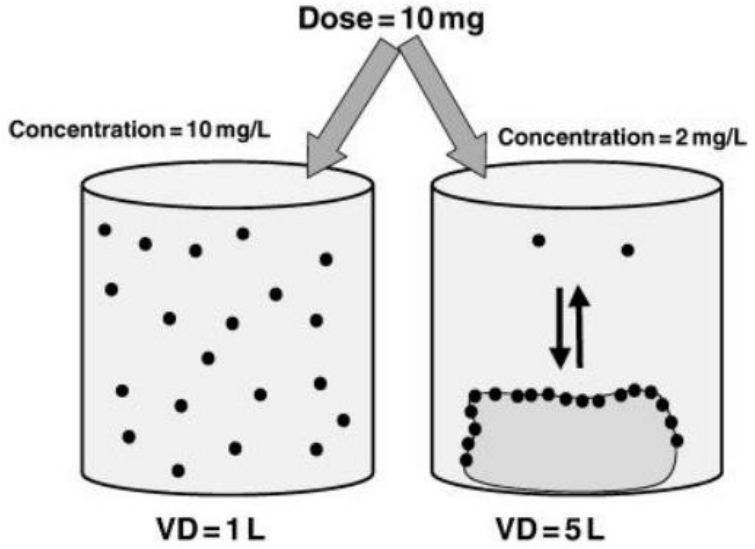
Low Vd (<5 L) → The drug remains mostly in the plasma (e.g., hydrophilic, protein-bound drugs).

Volume of distribution (Vd)

- Each drug is uniquely distributed in the body. Some distribute mostly into fat, others remain in ECF, & some bound extensively to specific tissues.
- **Many acidic drugs (e.g. warfarin, aspirin)** are highly protein-bound and thus have a **small** apparent VD.
- **Many basic drugs (eg, amphetamine)** are extensively taken up by tissues and thus have an apparent VD **larger** than the volume of the entire body.

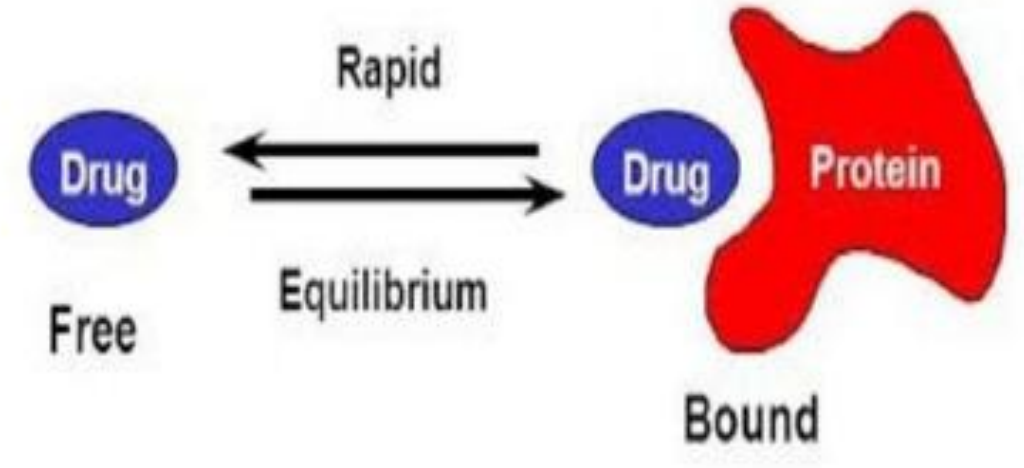
Volume of distribution (Vd)

- For a drug that is highly tissue-bound, very little drug remains in circulation; thus, plasma concentration is ……. and the VD is ……...
- Drugs that remain in circulation tend to have a …… VD.



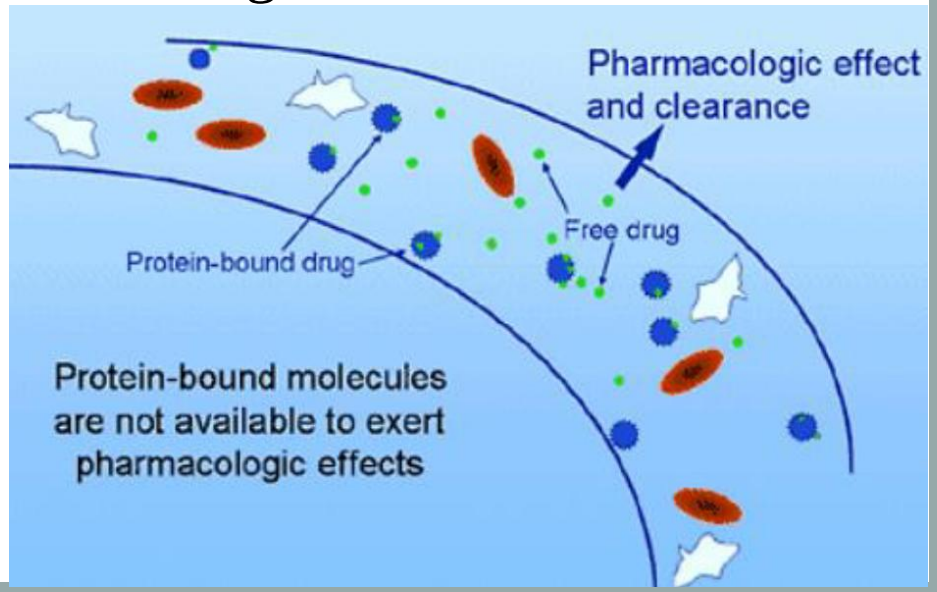
Binding drugs to proteins in blood

- In the bloodstream, drugs are transported partly in solution as free (unbound) drug and partly reversibly bound to blood components.
- The most important plasma proteins that interact with drugs are albumin, alpha-1 acid glycoprotein, and lipoproteins



Binding drugs to proteins in blood

- Only unbound drug is available for passive diffusion to extravascular or tissue sites where the pharmacologic effects of the drug occur.
- Thus, the unbound drug concentration in systemic circulation typically determines drug concentration at the active site and thus efficacy of the drug.



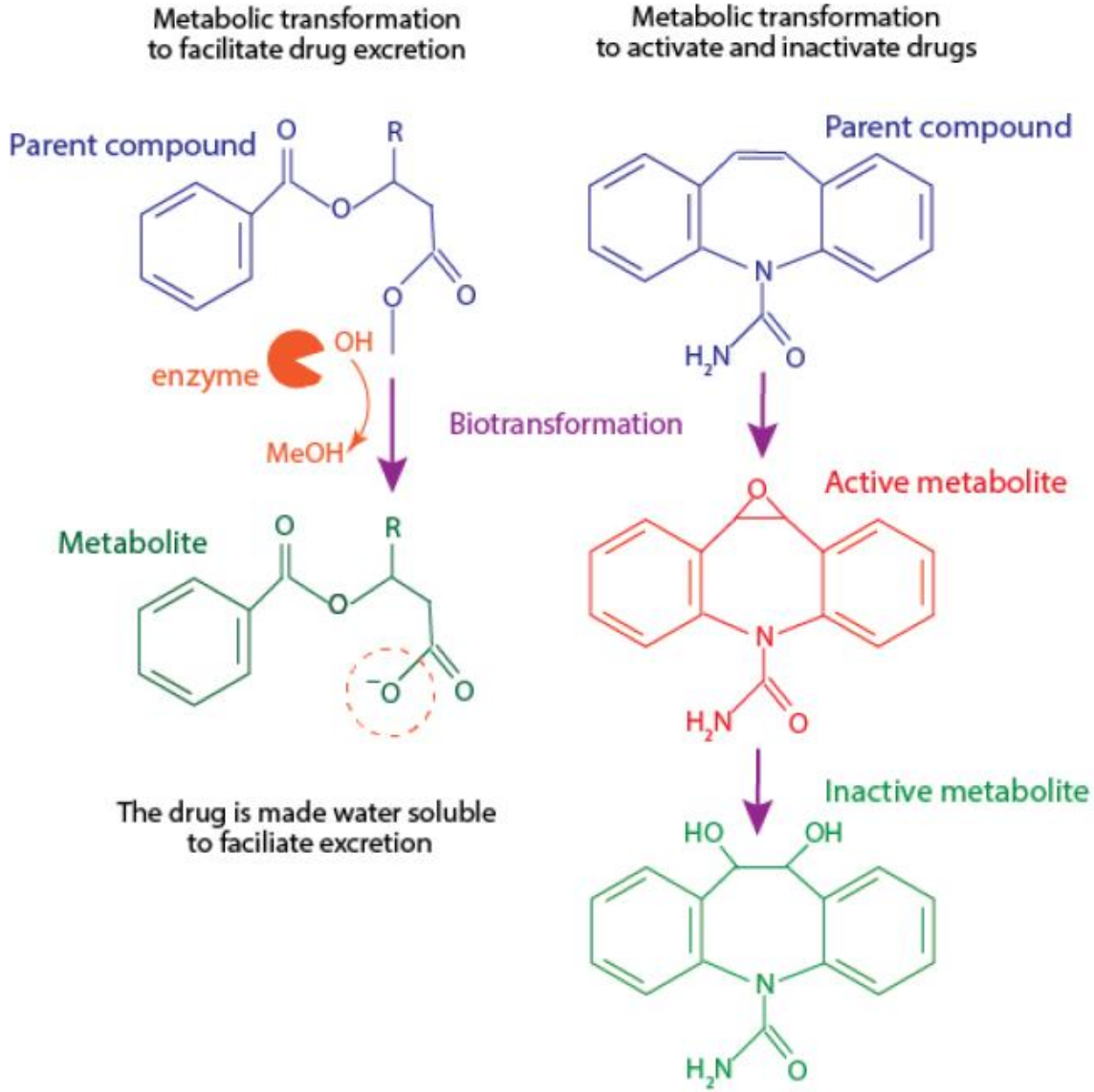
Accumulation of drugs in peripheral compartments

- Accumulation of drugs in tissues or body compartments can prolong drug action because the tissues release the accumulated drug as plasma drug concentration decreases.
- Some drugs accumulate within cells because they bind with **proteins, phospholipids, or nucleic acids**.

Drug metabolism

- Drug metabolism, also known as biotransformation, is the process by which the body chemically modifies drugs to **facilitate their elimination** or **activates prodrugs.**
- The products form after biotransformation are called "**drug metabolites**".
- It primarily occurs in the **liver**.

Drug metabolism



Phases of drug metabolism

Drug metabolism occurs in two major phases:

Phase I: Functionalization reactions

- Primarily carried out by cytochrome P450 (CYP) enzymes in SER of liver.

Reactions include:

- **Oxidation**
- **Reduction**
- **Hydrolysis**

Phases of drug metabolism

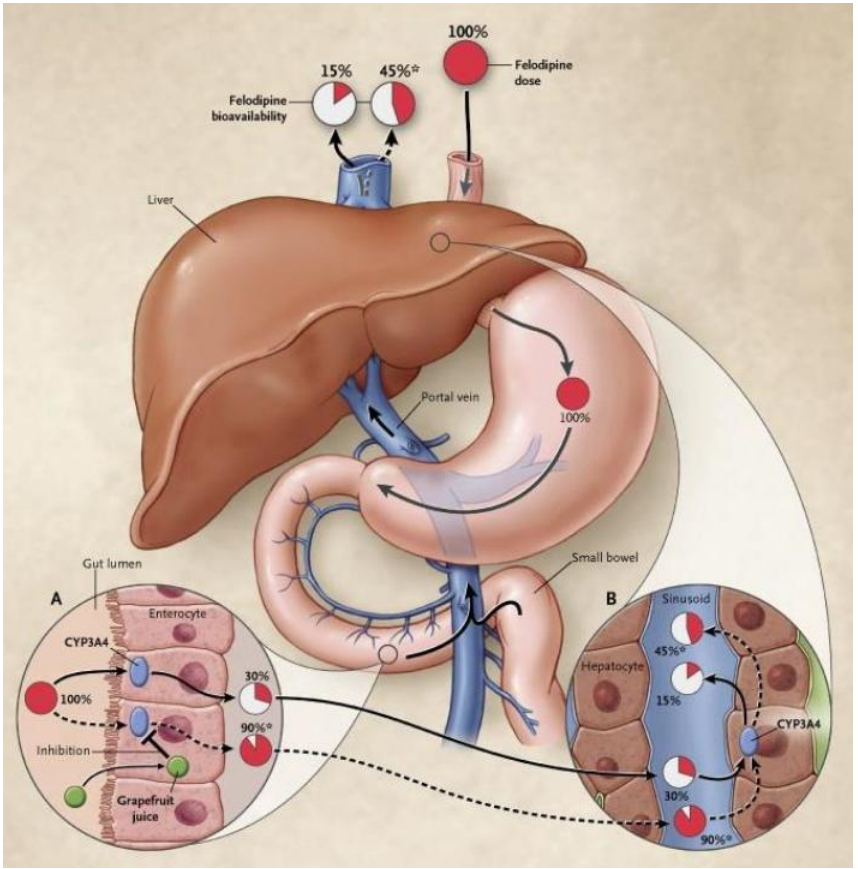
Phase II: Conjugation reactions

- Involves the attachment of polar molecules to the drug or its Phase I metabolites to enhance water solubility and excretion.
- **Common conjugation reactions:**

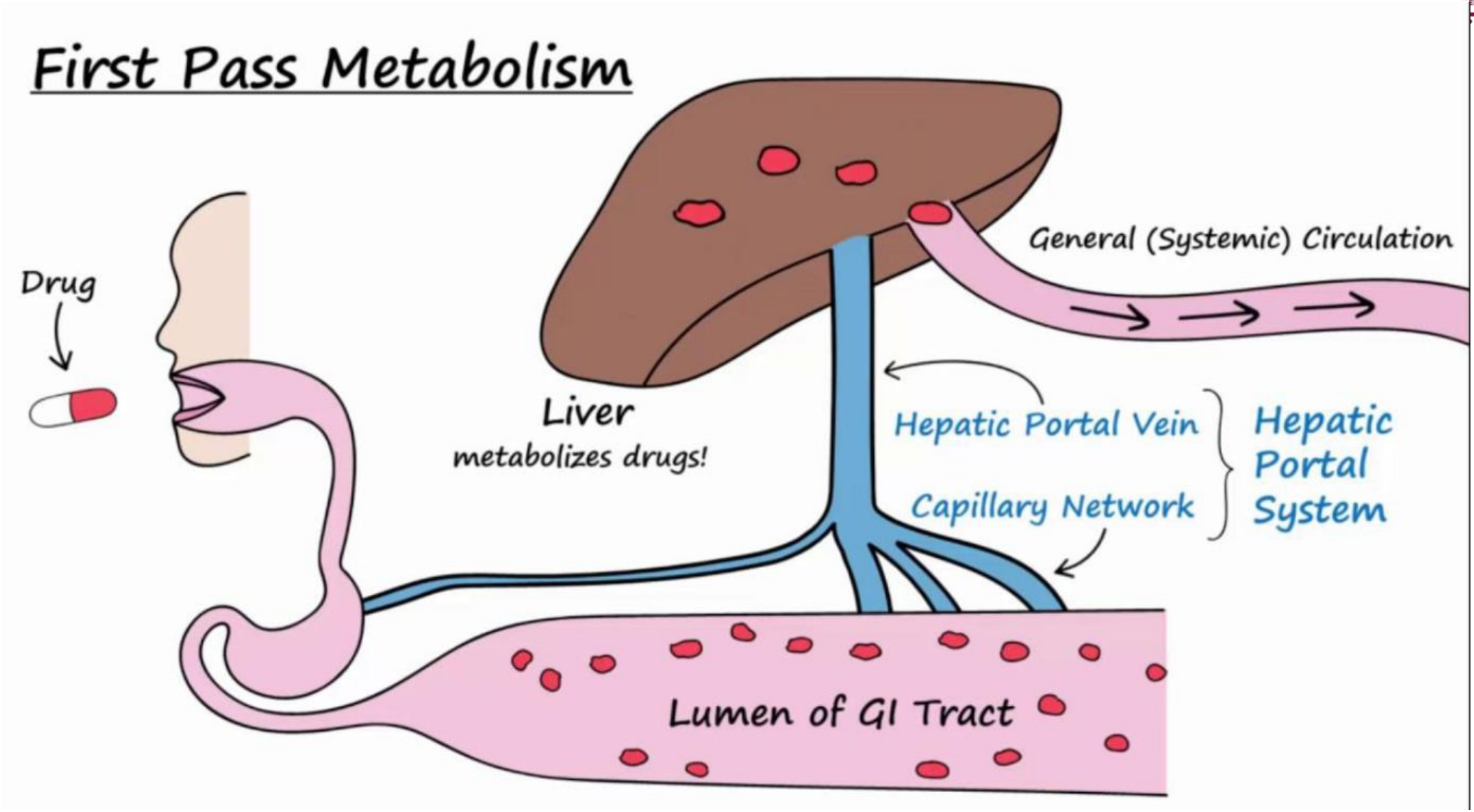
1. **Sulfation**
2. **Glutathione conjugation**
3. **Acetylation**
4. **Methylation**

Site of drug metabolism

- **The most important organ for drug metabolism is the liver.**
- **The kidneys play an important role in the metabolism of some drugs.**



Site of drug metabolism



Factors affecting drug metabolism

Several factors influence the rate and extent of drug metabolism:

1. **Genetic variability:** Polymorphisms in drug-metabolizing enzymes affect drug response.
2. **Age:** Neonates and elderly individuals have reduced metabolic enzyme activity.
3. **Liver diseases:** Hepatic diseases (e.g., cirrhosis, hepatitis) impair drug metabolism and prolong drug effects.
4. **Enzyme induction and inhibition**
5. **Diet and environmental factors**
6. **Drug-Drug interactions**