Pharmacokinetics (PK): Drug Elimination

1. **Principles:**

   In Pharmacokinetics, **Elimination** is the umbrella term for the irreversible removal of a drug from the body. It is the sum of two processes:

$$\text{Elimination} = \text{Metabolism (Biotransformation)} + \text{Excretion}$$

2. **The Main Exit: Renal Excretion**

The kidney is the primary organ for excreting small, water-soluble drugs and metabolites (like the HVA: Homovanillic acid produced from L-Dopa/Dopamine example).

There are three distinct steps in the nephron that determine the final amount of drug in the urine:

- **Glomerular Filtration**: Passive "sieving." Only the unbound fraction (f_u) of the drug is filtered. Large proteins and biologics are usually too big to pass.
- **Active Tubular Secretion**: A "pumping" mechanism in the proximal tubule. Even protein-bound drugs can be stripped off and pumped into the urine here. This is a saturable process.
- **Passive Tubular Reabsorption**: The "recycling" phase. Lipophilic, non-ionized drugs sneak back into the blood. This is where pH-partitioning happens—remember, changing urine pH can "trap" a drug in the tubule to speed up its exit.

3. **The "Back Door": Biliary Excretion**

Some drugs, especially large polar molecules or those conjugated with glucuronic acid (Phase II), are pumped into the bile by the liver and dumped into the gut.

- **Enterohepatic Recirculation:** A drug is excreted in the bile into the intestine, but then gut bacteria "un-conjugate" it, making it lipophilic again. The drug is then re-absorbed back into the blood.
- **Result:** This creates a second peak in the plasma concentration-time curve and significantly extends the half-life of the drug.

4. **The Mathematics of "The Exit"**

To describe elimination quantitatively, we use three key parameters:

A. Elimination Rate Constant (ke): This represents the fraction of drug removed per unit of time.

$$\text{Rate of elimination} = k_e \cdot C$$

B. Clearance (Cl)

The most important parameter. It is the **volume of plasma** cleared of the drug per unit of time (e.g., mL/min).

$$Cl = V_d \cdot k_e$$

C. Half-life ($t_{1/2}$)

The time required for the plasma concentration to decrease by 50%.

$$t_{1/2} = \frac{0.693}{k_e} = \frac{0.693 \cdot V_d}{Cl}$$

5. Kinetics: First-Order vs. Zero-Order

Most drugs follow **First-Order Kinetics**, but a few troublesome ones (like Alcohol or high-dose Aspirin/Phenytoin) follow **Zero-Order**.

Feature	**First-Order (Linear)**	**Zero-Order (Non-linear)**
Rate	Proportional to concentration.	**Constant** regardless of concentration.
Half-life	Constant.	Changes with dose.
Analogy	A percentage of the crowd leaves.	A fixed number of people leave (bottleneck).

6. Case Study: L-Dopa Metabolites

How L-Dopa is eliminated:

1. **Metabolism:** It is first decarboxylated to Dopamine, then oxidized by **MAO** and **COMT**.
2. **Excretion:** The final metabolites (like **Homovanillic Acid - HVA**) are highly polar organic acids.
3. **Mechanism:** They are eliminated via **Glomerular Filtration** and **Active Tubular Secretion** in the kidney.