EXCRETION OF DRUGS

❖ Definition

- Excretion is defined as a process whereby drugs or metabolites are irreversibly transferred from internal to external environment through renal or non-renal route.
- Excretion, along with metabolism and tissue redistribution, is important in determining both the duration of drug action and the rate of drug elimination.
- **Clearance (CL)-**
  - → The clearance of a drug is the theoretical volume of plasma from which the drug is completely removed in unit time.
  - → It can be calculated as:

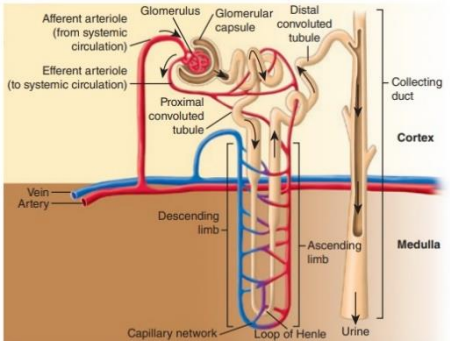
$$CL = \frac{rate\ of\ elemination}{C}$$

where *C* is the plasma concentration.

- **Plasma half-life -** The Plasma half-life (t½) of a drug is the time taken for its plasma concentration to be reduced to half of its original value.
- **Principal organs involved**:
  - i) Kidneys (Renal Excretion)
  - ii) Bile (Biliary Excretion)
  - iii) Lungs (Pulmonary Excretion)
  - iv) Saliva (Salivary Excretion)
  - v) Milk (Mammary Excretion)
  - vi) Sweat (Skin Excretion)

1. Kidney

- Drugs are eliminated from the body primarily by the kidneys.
- The principal renal mechanisms that are involved in the excretion of drugs are:
  - (a) Glomerular filtration
  - (b) Active tubular secretion
  - (c) Passive tubular reabsorption



i) Glomerular filtration

- The ultrastructure of the glomerular capillary wall is such that it permits a high degree of fluid filtration while restricting the passage of compounds having relatively large molecular weights.
- This selective filtration is important in that it prevents the filtration of plasma proteins (e.g., albumin) that are important for maintaining an osmotic gradient
- Several factors, including molecular size, charge, and shape, influence the glomerular filtration of large molecules.
- As the ultrafiltrate is formed, any drug that is free in the plasma water, i.e not bound to plasma proteins or RBC will be filtered as a result of the driving force provided by cardiac pumping.
- All unbound drugs will be filtered as long as their molecular size, charge, and shape are not excessively large.
- Compounds with 20 Å to 42Å may undergo glomerular filtration.

ii) Active Tubular secretion

- Tubular secretion is **the transfer of materials from peritubular capillaries to the renal tubular lumen**
- The tubular secretion which is carried out at the level of the proximal tubule is an active process.
- It is carrier mediated process which requires energy for transportation of compounds against conc. gradient
- Two secretion mechanisms are identified.
  - (a) System for secretion of organic acids/anions e.g. Penicillin, salicylates etc
  - (b) System for organic base / cations e.g. morphine, mecamylamine hexamethonium

iii) **Passive tubular reabsorption**

- Tubular reabsorption is **the process that moves solutes and water out of the filtrate and back into your bloodstream**
- Drugs which are present in the glomerular filtrate can be reabsorbed in the tubules.
- Only un-ionized molecules are available for reabsorption.
- Many drugs are either weak bases or acids and therefore the pH of the filtrate can greatly influence the extent of tubular re-absorption for many drugs. When urine is acidic, weak acid drugs tend to be reabsorbed. Alternatively when urine is more alkaline, weak bases are more extensively reabsorbed.
- Making the urine more acidic can cause less reabsorption of weak bases or enhanced excretion.
- In the case of a drug overdose it is possible to increase the excretion of some drugs by suitable adjustment of urine pH. For example, in the case of pentobarbital (a weak acid) overdose it may be possible to increase drug excretion by making the urine more alkaline with sodium bicarbonate injection.

2. **Biliary Excretion**
   - Biliary excretion involves **active secretion of drug molecules or their metabolites from hepatocytes into the bile**
   - Transporters are present in the canalicular membrane of the hepatocyte, and these actively secrete drugs and metabolites into bile. e.g. the organic anion transporting polypeptides (OATPs), the P-glycoprotein transport system and the multidrug resistance-associated proteins (Mrps).
   - Drug in bile enters the gastrointestinal tract after storage in the gallbladder. It may then be excreted from the body by the stools.
   - A drug excreted in bile may be reabsorbed from the gastrointestinal tract or a drug conjugate may be hydrolyzed by gut bacteria, liberating original drug which can be returned to the general circulation. Such recycling may continue (enterohepatic cycle or circulation) until the drug either undergoes metabolic changes in the liver, is excreted by the kidneys, or both.
   - Such enterohepatic recycling, if extensive, may prolong significantly the presence of a drug (or toxin) and its effects within the body prior to elimination by other pathways.
   - Orally administered activated charcoal and/or anion exchange resins have been used clinically to interrupt enterohepatic cycling and trap drugs in the gastrointestinal tract.
   - Cholestatic disease states, in which normal bile flow is reduced, will influence drug elimination by this route resulting in increased risk of drug toxicity.
3. **Pulmonary excretion**
   - Gases and other volatile substances such as general anaesthetics that enter the body primarily through the respiratory tract can be expected to be excreted by this route.
   - No specialized transport systems are involved in the loss of substances in expired air; simple diffusion across cell membranes is predominant.
   - The rate of loss of gases is not constant; it depends on the rate of respiration and pulmonary blood flow.
   - The degree of solubility of a gas in blood also will affect the rate of gas loss.
   - Gases such as nitrous oxide, which are not very soluble in blood, will be excreted rapidly.
   - Ethanol, which has a relatively high blood gas solubility, is excreted very slowly by the lungs.
4. **Salivary excretion**
   - The pH of saliva varies from 5.8 to 8.4. Unionized lipid soluble drugs are excreted passively.
   - The bitter taste in the mouth of a patient is indication of drug excreted.
   - Compounds excreted in saliva are Caffeine, Phenytoin, Theophylline.
5. **Mammary excretion**
   - Milk consists of lactic secretions which is rich in fats and proteins.
   - Excretion of drug in milk is important as it gains entry in breast feeding infants.
   - pH of milk varies from 6.4 to 7.6. Free un-ionized and lipid soluble drugs diffuse passively.
   - Highly plasma bound drug like Diazepam is less secreted in milk.
   - Amount of drug excreted in milk is less than 1% and fraction consumed by infant is too less to produce toxic effects.
   - Some potent drugs like barbiturates and morphine may induce toxicity.

6. Skin excretion

- Drugs excreted through skin via sweat follows pH partition hypothesis.
- Excretion of drugs through skin may lead to urticaria and dermatitis.
- Compounds like benzoic acid, salicylic acid, alcohol and heavy metals like lead, mercury and arsenic are excreted in sweat.

❖ **Excretion Pathways, Transport Mechanisms & Drug Excreted**

Excretory route	Mechanism	Drug Excreted
Urine	GF, ATS, PTR	Free, hydrophilic, unchanged drugs/ metabolites of MW< 300
Bile	Active secretion	Hydrophilic, unchanged drugs/ metabolites/ conjugates of MW >500
Lung	Passive diffusion	Gaseous &volatile, blood & tissue insoluble drugs
saliva	Passive diffusion Active transport	Free, unionized, lipophilic drugs. Some polar drugs
Milk	Passive diffusion	Free, unionized, lipophilic drugs (basic)
Sweat	Passive diffusion	Free, unionized lipophilic drugs