PHARMACOKINETICS 4

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Pharmacokinetics

what the body does to the drug?

- Absorption
- Distribution
- Metabolism
- Excretion.

EXCRETION OF DRUGS

- **Kidney:** most important organ for excretion
- Excretion occurs through:

1. Glomerular filtration
2. Proximal convoluted tubules (PCT)
3. Distal convoluted tubules (DCT)

1-Glomerular filtration

- All free drug molecules whose size is **less** than the glomerular pores are filtered into Bowman's capsule.

2-Proximal convoluted tubules (PCT)

Active secretion occurs either through

- acid carrier e.g. for penicillin, probenicid, salicylic acid.
- basic carrier for amphetamine and quinine.

3-Distal convoluted tubules (DCT)

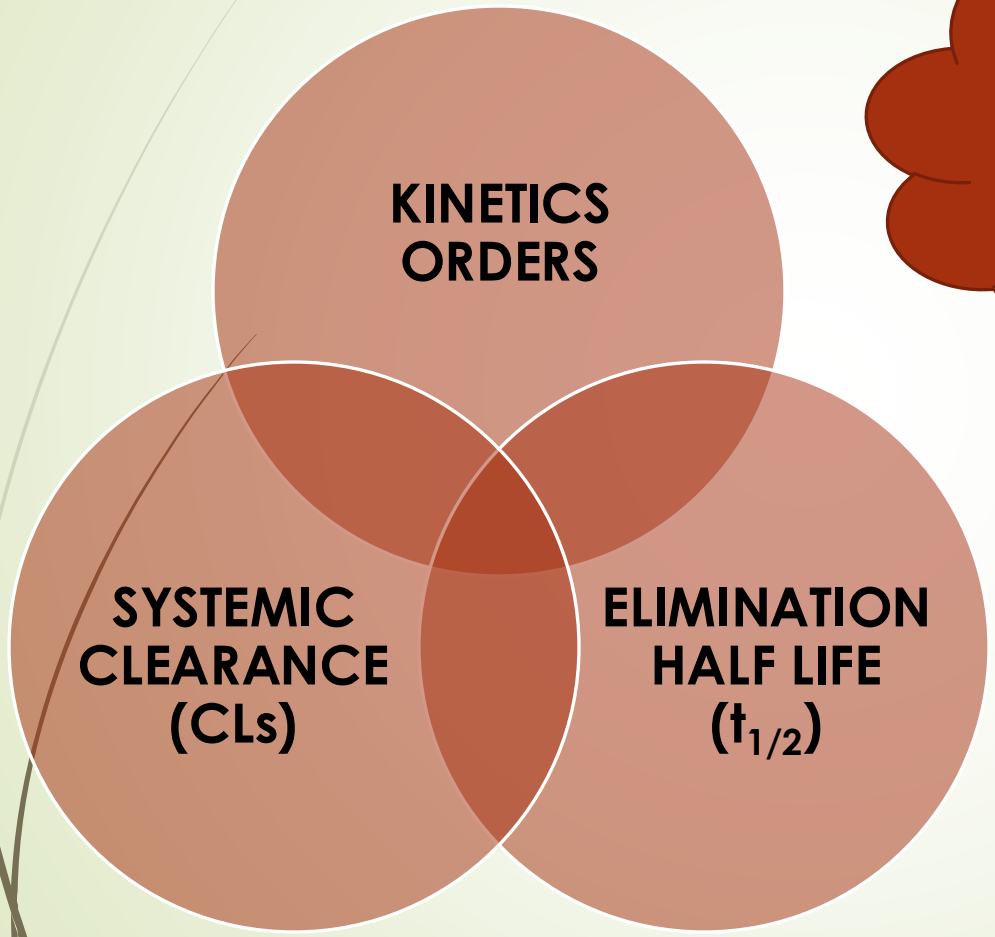
- Lipophilic drugs may be reabsorbed back to systemic circulation.
- *Alkalinization of urine* keeps acidic drugs ionized and increases their excretion.
- *Acidification of urine* keeps basic drugs ionized and increases their excretion.

Other sites of excretion:

- **Bile:** e.g. Doxycycline, Azithromycin.
- **Lungs** e.g. Volatile anesthetics.
- **Saliva** e.g. Iodides.
- **Sweat** e.g Rifampicin.
- **Milk**: this is important in lactating mothers.

PARAMETERS OF ELIMINATION

refer to the quantitative measures that describe how a drug is removed from the body, mainly through metabolism and excretion



KINETICS ORDERS

describes how the **rate of drug elimination** changes in relation to the **drug concentration** in the body

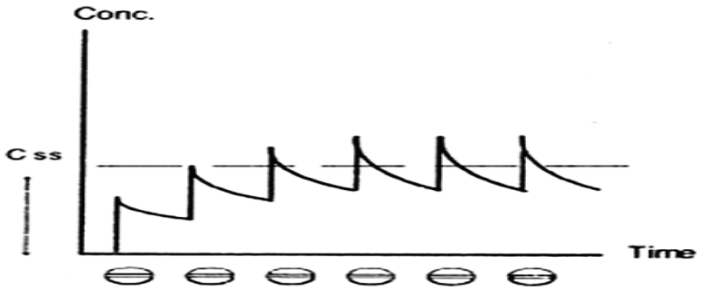
First order **kinetics**

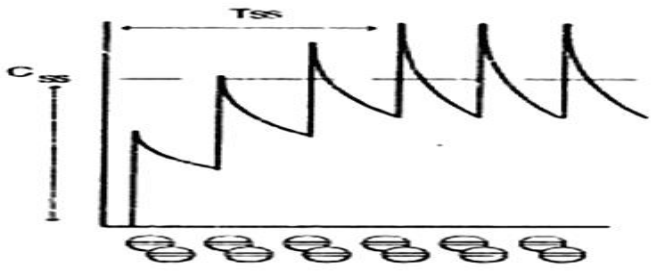
Zero order kinetics

Mixed-Order (Michaelis–Menten) Kinetics

First order kinetics (most drugs):

- Rate of elimination is directly proportionate to the blood concentration of drugs (***constant percentage*** of the drug is eliminated per unit of time)
- **Constant "$t_{1/2}$"**
- Repeated dosing increases drug concentration and accordingly the rate of elimination increases till the rate of administration equals the rate of elimination.
- Css can be reached after 4-5 $t_{1/2}$
- Css is directly proportionate to the dose.

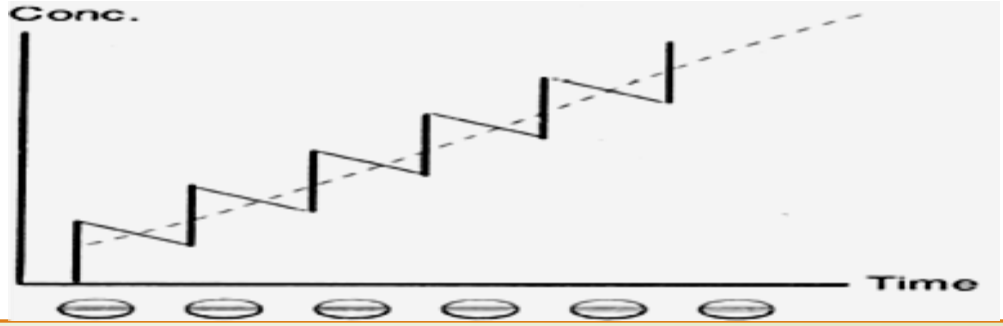




↑ dose ⟶ ↑ Css

Zero order kinetics
(phenytion and salicylate)

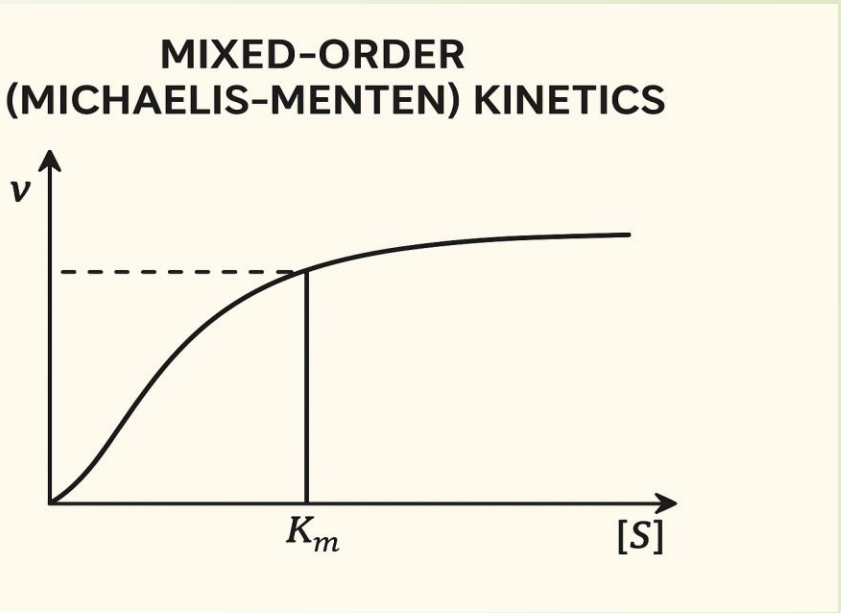
- Rate of drug elimination is constant i.e. ***constant amount*** of drug is eliminated per unit of time.
- "$t_{1/2}$" (half life) is not constant.
- No Css is reached by repeated dosing.
- Any change of the dose may cause toxicity.



Mixed-Order (Michaelis–Menten) Kinetics

Some drugs follow 1st order kinetics in small dose and zero order kinetic at large doses i.e. the elimination mechanism is said to be saturated (saturation kinetics).

- e.g, Theophylline (at high doses)



At low [S]: The curve rises almost linearly → follows first-order kinetics.(Rate ∝ [S])→ The enzyme is not saturated; most active sites are free.

At high [S]: The curve plateaus, approaching a maximum rate *V*max

Vmax → The enzyme becomes saturated; adding more substrate doesn't increase the rate → Reaction follows zero-order kinetics

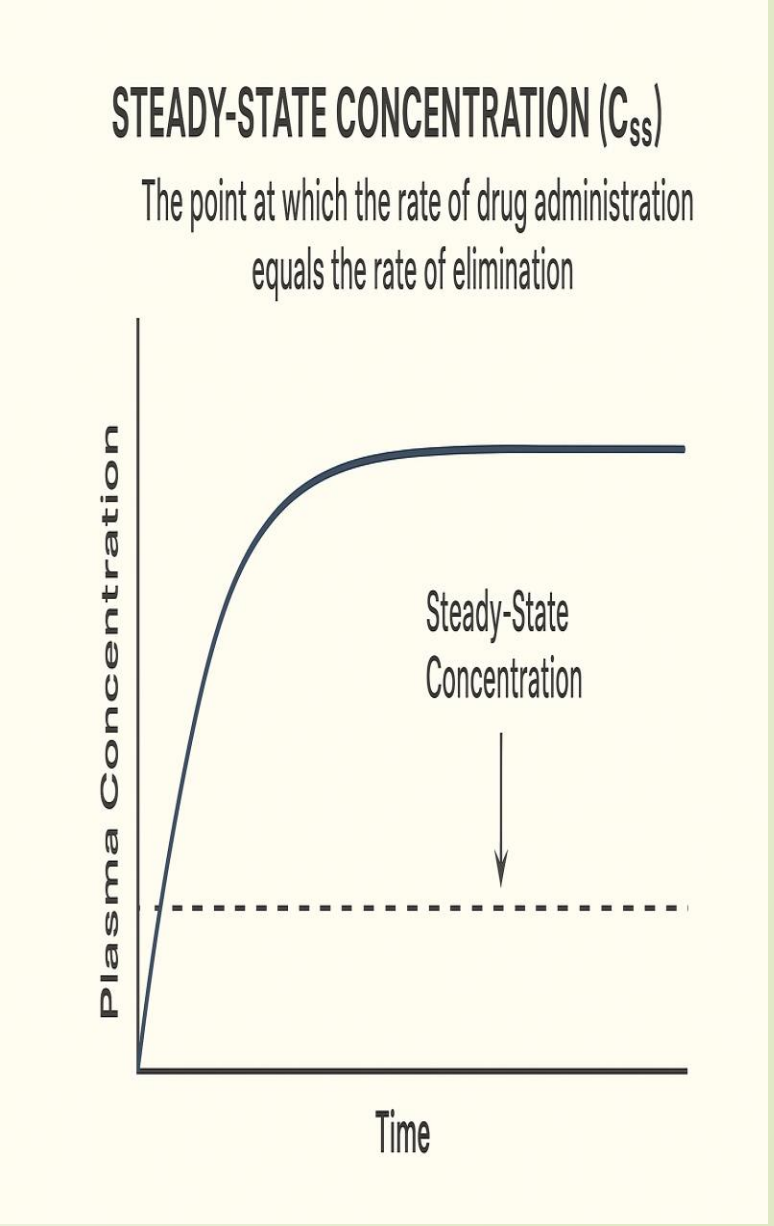
Steady-State Concentration (Css)

- is the point during repeated dosing or continuous infusion when the rate of drug administration equals the rate of elimination (meaning plasma concentration stays constant)
- Reached after about 4–5 half-lives.
- Depends on the dose rate and clearance.
- Css= Rate of drug administration Clearance
- Increasing the dose rate raises Css
- changing half-life affects how long it takes to reach Css, not the final level.
- Clinical Importance

Ensures effective and safe drug levels.

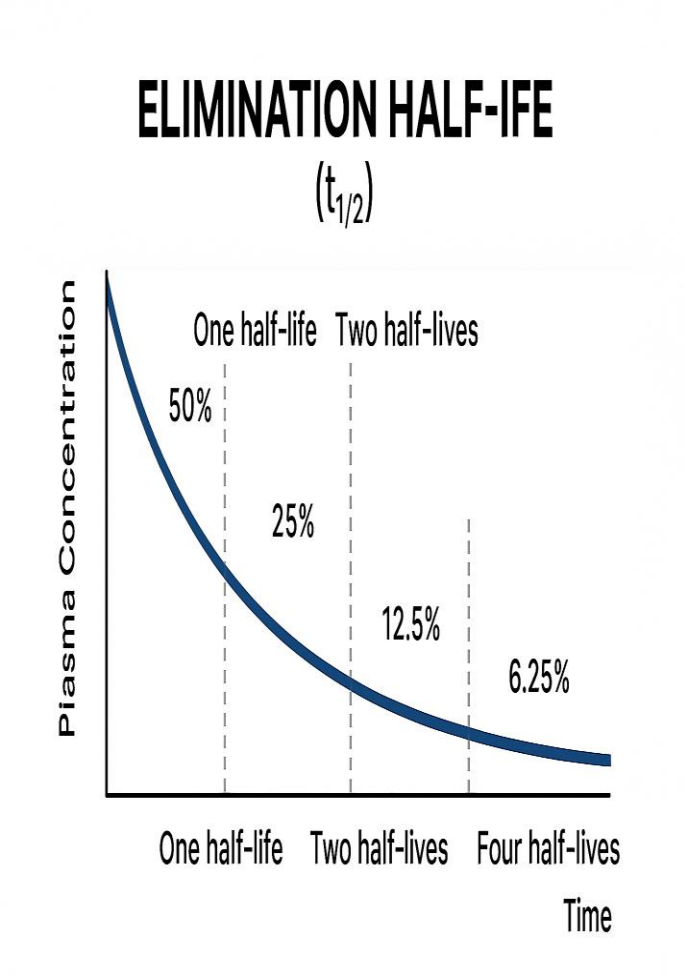
Used for maintenance dosing.

Important in IV infusions and chronic therapy (e.g., anticonvulsants, antibiotics).



ELIMINATION HALF LIFE ($T_{1/2}$)

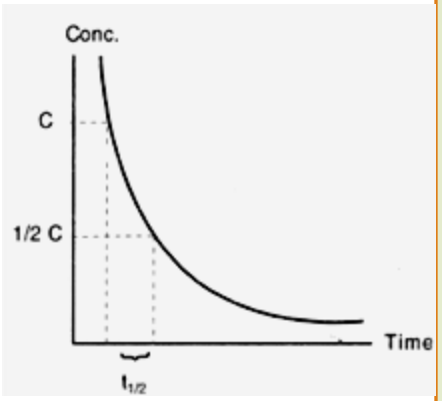
- It is the time required to reduce the plasma concentration of the drug to half the initial concentration (the time required for drug concentration to be changed by 50%).
- $T_{1/2} = 0.7\ V_d/CLs$



Importance of elimination $T_{1/2}$:

- It determines the dosage interval (T).
- It indicates time required to attain

  Css (about 4-5 $t_{1/2}$):
- If "**$t_{1/2}$**"is very short (minutes),



the drug should be given by IV infusion [dopamine].

- If "**$t_{1/2}$**"is long [digoxin], the drug should be administered in loading dose followed by maintenance dose

Factors affecting elimination "$t_{1/2}$":

- State of eliminating organs i.e. liver & kidney function.
- Delivery of drugs to the eliminating organs: affected by plasma protein binding and Vd of the drug.

SYSTEMIC CLEARANCE (CLs)

- It is the volume of fluid cleared from the drug per unit of time.
- **Systemic CLs** = Renal clearance (CL_r) + non-renal clearance (CLnr)

Significance of clearance

- Calculation of the maintenance dose

- **Loading dose:** The dose required to achieve a desired plasma concentration (desired Css) rapidly, followed by routine maintenance dose.

Loading dose = Vd ×TC

- **Maintenance dose:** The dose given to maintain the desired Css.

Maintenance dose = CLs **×TC (**Target concentration).

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Thank you!