

1/10 EXCRETION.

- Passage out of systemically absorbed drug.
- Excreted unchanged or as metabolites

• Normal GFR → 125 ml/min.

factors affecting glomerular filtration

- molecular size (inversely proportional)
- Plasma protein binding (inversely)
- Renal Blood flow (direct).

HOFFMAN'S ELIMINATION Question

Renal
Biliary
Alveolar

Major routes of excretion.

Sweat
Saliva.
Milk.

Minor routes.

Driving force → capillary hydrostatic pressure.

Tubular reabsorption

- Passive diffusion
 - lipid solubility (directly proportional)
 - Ionization of drug (inversely proportional)

Renal Excretion

Kidney - most important organ of excretion.

Net renal excretion = (glomerular filtration + tubular secretion) - tubular reabsorption.

JIVA

Alkalinization: Rx of poisoning of barbiturates and salicylates (acidic drugs) to increase & prevent reabsorption.

acidification → not prevented clinically due to side effects Cardio toxicity and

3 principle processes.

- Glomerular filtration
- Tubular secretion
- Tubular reabsorption.

Glomerular filtration

Glomerular capillaries → large pore → non-protein bound drugs filtered out.

Active Tubular Secretion

Site: Proximal tubule.

- Transporter mediated
- Active transfer of organic acids and bases.
- Energy dependant

(1) → Depends on renal blood flow

Transporters

- OATP → organic acid transport
- OCT → organic base transport
- P-glycoprotein, MRP2
↳ efflux transporters.

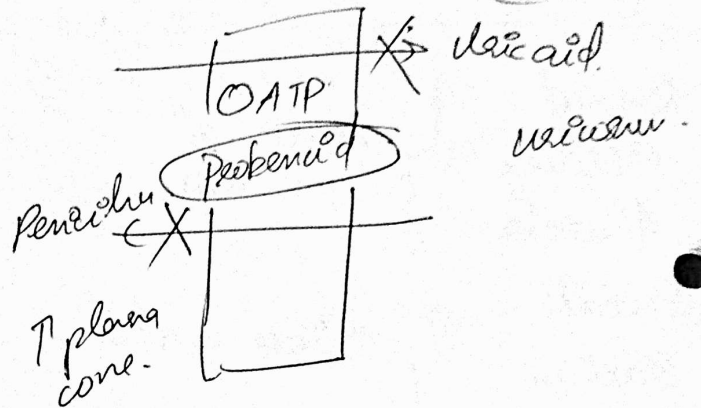
Organic acid transport

Through OATP
for acidic drugs.

Penicillin, probenecid, uric acid, salicylates, Nefopam, methohexate.

Eg: Probenecid & uric acid and Penicillin

On Probenecid (used in gout)
↳ High affinity for OATP.
Block active transport of both;
reduce penicillin bioaction and
uric acid reabsorption (Question)



Organic base transport

- Through OCT
- for basic drugs.
- Endogenous compounds (reabsorbed).
- Drugs & their metabolites (secreted).

eg: Furosemide, Thiazides, Ameloxide, Quinine, Karamine.

Active tubular secretion

- B/Directional.
- Drugs utilizing same active transport compete with each other.

Biliary Excretion

- Larger molecules eliminated in bile.
- 90% reabsorbed.
- High polarity drugs } Excreted
- Metabolites
- Active process.
- Transporters - OATP, OCT, MRP2, P-gp.

Eg: Cephazolin, ampicillin, rifampicin, OCP, tetracycline.

Question

Enterohepatic circulation

Phenomenon of cycling of drug b/w intestine & liver.
Eg: cardiac glycosides, Rifampin, chlorpromazine, Indomethacin

Advantages:

- Prolongation of drug action.
eg: OCP, Rifampicin.

Enzyme Inducers. Pataka question

Flucelar Excretion.

- simple diffusion
- Gases, volatile liquids
(general anesthetics, alcohol)

Depends on % of drug
partial pressure in blood.

Saliva, sweat

Minor route.

- Lithium, rifampicin,
heavy metals.

Milk Excretion.

Small amounts only reach
infant

- passive diffusion
- lower pH (6.6); so
basic drugs concentrated
in milk.

3 PK parameters

- Bioavailability
- V_d
- clearance.

Question

Clearance (Short Note)

- Measure of body's efficiency
in eliminating drug from
systemic circulation

- Theoretical volume of plasma
from which the drug is
completely removed in unit
time.

$$CL = \frac{\text{Rate of elimination}}{\text{Plasma concentration}}$$

Plasma half life. (repeated short note)

- The plasma half-life of
a drug is the time taken
for the plasma concentration
to be reduced to half of its
original value.

$$\begin{aligned} \text{Elimination } t_{1/2} &= \frac{\text{natural logarithm of 2}}{k} \\ &= \frac{0.693}{k} \end{aligned}$$

k → elimination rate constant

$$k = \frac{CL}{V_d}$$

$$t_{1/2} = 0.693 \times \frac{V_d}{CL}$$

The fractional amount remaining of the % of drug remaining after a given no. of half lives.

Half lives (n)	Drug Remaining (%)	Drug Eliminated (%)
0	100	0.
1	50	50
2	25	75.
3	12.5	87.5.
4	6.25.	93.75.
5	3.125.	96.875.

At end of 5 half lives, almost 97% of the drug is eliminated.

Uses of half life

- As a guide for the time taken for a drug to get eliminated from the body
- As a guide for the time to reach steady state.
- As a guide to the relationship between loading dose and maintenance dose.

Half life of some representative drug.

Paracetamol → 2 hr.

Penicillin G → 30 min

Digoxin → 40 hr.
Digitoxin → 7 days.

1st order kinetics. (Question)

- constant amount of drug is eliminated in unit time.
- Rate of elimination is constant irrespective of drug concentration
↳ cumulative toxicity

→ $T_{1/2}$ is never constant; changes with plasma concentration.

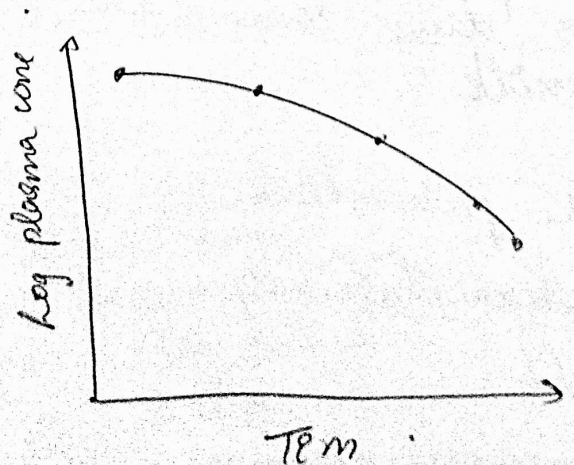
CC decreases with increase in concentration.

Eg: Alcohol.

200 $\xrightarrow[50\mu g]{2hr.}$ 150 $\xrightarrow[50\mu g]{2hr.}$ 100
50 $\downarrow$ 50

Other names:

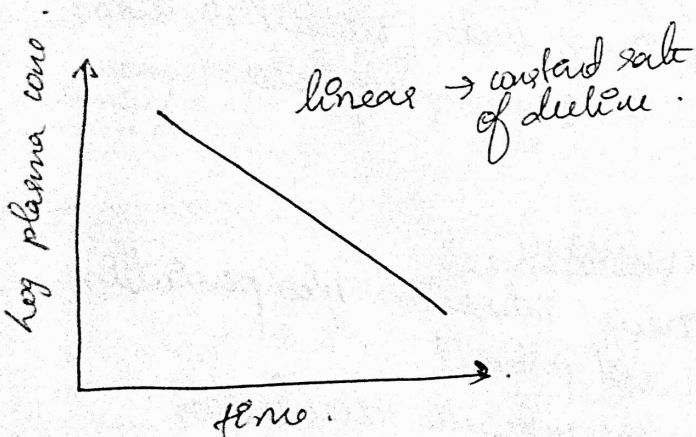
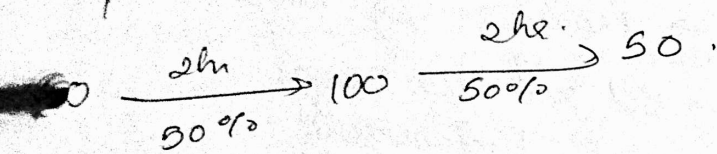
- Non linear.
- Michaelis menten elimination
- capacity limited elimination.



non linear curve.

First order kinetics (Exam Qn)

- constant fraction of drug is eliminated in unit time.
- Rate of elimination proportional to drug concentration.
- $T_{1/2}$ remains constant
- Clearance remains constant
- Eg: Majority of drugs (paracetamol, penicillin etc)



Eg: Phenytoin, warfarin, theophylline, salbutamol.

Steady state plasma concentration (C_{ss}) - Plateau principle.

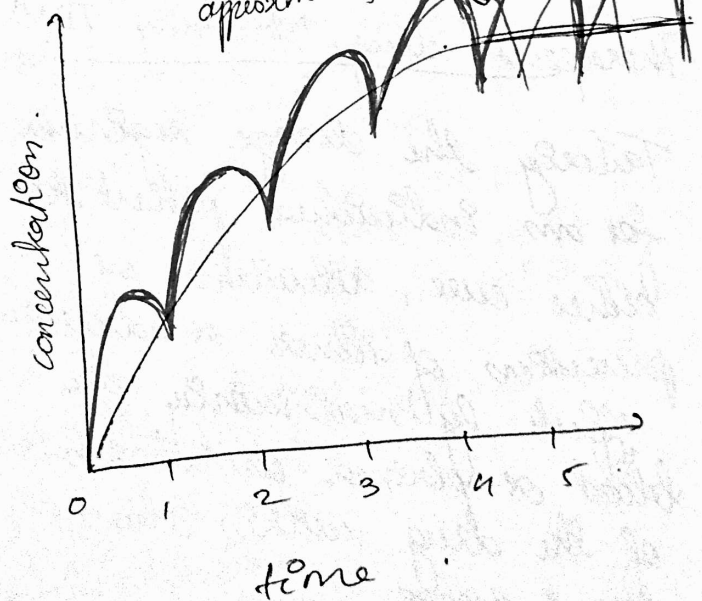
Is the plasma concentration of the drug at which rate of absorption equals the rate of elimination.

$$C_{ss} = \frac{\text{dose rate}}{CL}$$

→ C_{ss} is achieved after 4-5 $t_{1/2}$

→ In steady state, the plasma concentration rises and falls within the therapeutic range.

Steady state attained approximately after 4 half lives.



Saturation kinetics

- Mixed order kinetics / Non-linear elimination
- Elimination of some drugs approach saturation over therapeutic range
- Due to saturation of metabolizing enzymes or elimination process
- Kinetics change from 1st order to zero order at higher doses

Loading dose.

- This is a single or few quickly repeated doses given in the beginning to attain target concentration rapidly

→ Mainly for drugs with high V_d
Does not depend on clearance.
Loading dose = $\frac{\text{target plasma con.} \times V_d}{F}$

F
→ Bioavailability

Maintenance dose:

→ The dose is to be repeated at specified intervals after the attainment of C_{ss} to maintain the same by balancing elimination.

→ Depends on clearance.

→ Dose rate = $\frac{\text{target } C_{ss} \times CL}{F}$

Therapeutic drug Monitoring TDM

Tailoring the dosage regimen for an individual patient for either cure, alleviation or prevention of illness or adverse effects by maintaining the level or plasma concentration of the drug within the target range.

Indications - TDM

- drugs with low safety margin.
- If individual variations are large.
- Potentially toxic drug in case of renal failure.

→ In case of poisoning
→ To check no-compliance of patient.
→ Therapeutic failure
eg: antimicrobials.

No value - TDM

→ drugs whose response is easily measurable.

Eg: antihypertensives, hypoglycemics

→ Prodrugs Eg: Levodopa.

→ Hit and run drugs
eg: Paracetamol.

→ Drugs with irreversible action
eg: Organophosphates (person, pet, birds)

Questions

- Drug interaction b/w penicillin and procaine.
- enterohepatic circulation.
- clearance.
- Plasma half life.
- First order kinetics.
- Zero order kinetics.
- Mixed order kinetics.
- Steady state plasma concentration.