BIOPHARMACEUTICS

UNIT 5 NOTES

NON LINEAR PK

- INTRODUCTION
- FACTORS CAUSING NON LINEARITY
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- EXAMPLE OF DRUGS

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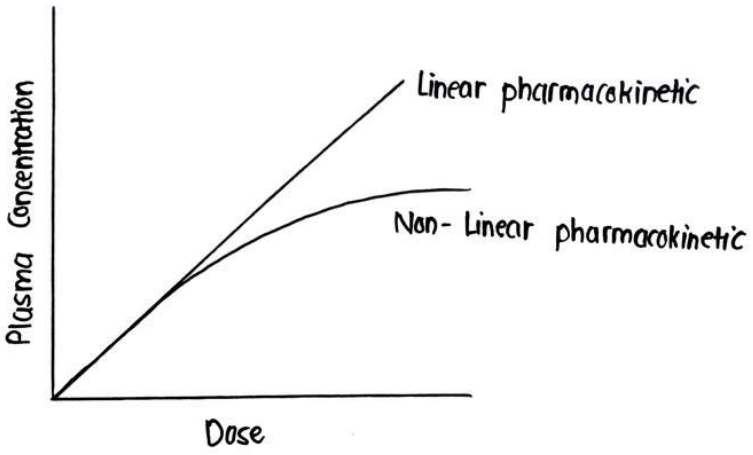
NON LINEAR PHARMACOKINETICS

- Non-linear pharmacokinetics refers to the condition when the rate of drug absorption, distribution, metabolism or excretion does not change proportionally with the administered dose.
- In other words:
  - A change in dose leads to a non-proportional change in plasma concentration, AUC or drug elimination.

KEY FEATURES OF NON LINEAR PK

PARAMETER	LINEAR PK (First Order)	NON LINEAR PK (Zero order/ Mixed)
Plasma Conc. vs Dose	Proportional	Disproportional
Clearance (CL)	Constant	Changes with dose
Half life ($t_{1/2}$)	Constant	Varies with dose
AUC (Area Under Curve)	Proportional to dose	Non-proportional
Elimination Rate	Increases with concentration	Becomes constant at high concentrations



FACTORS AFFECTING NON - LINEAR PHARMACOKINETICS

① SATURABLE (capacity - limited) METABOLISM

- Enzymes responsible for drug metabolism (e.g. CYP450 enzymes) can become saturated when drug concentration is high.
- Once saturation occurs, increasing the dose no longer increases metabolism proportionally.

Result :
- Clearance decreases as doses increases.
- Half - life increases with higher doses.

Example :
- Phenytoin (Antiepeliptic)
- Ethanol
- Theophylline

② Saturable Absorption

- Drugs that are absorbed via carrier-mediated transport in the GI tract can show non-linear PK when transporters are saturated.
- At high doses, the rate of absorption plateus.

Result:
- Bioavailability decreases at high doses.
- Non-proportional increase in plasma concentration.

Examples:
- Gabapentin
- L-Dopa

③ Saturable Plasma Protien Binding

- Drugs bind to plasma proteins (e.g. albumin), but binding sites are limited.
- At high drug concentrations, binding sites become saturated.

Result:
- More free drug is available → increased pharmacological effect and toxicity.
- Total plasma concentration may not reflect actual active concentration.

Examples:
- Valpoic Acid
- Salicyclates.

④ Saturable Renal Elimination (Secretion/ Reabsorption)

- Some drugs are actively secreted to or reabsorbed in the kidneys via carrier proteins.
- At high concentrations, these transport systems become saturated.

Result:
- Decreased renal clearance at high doses.
- Non-linear elimination kinetics.

Example:
- Penicillin
- Cephalosporins

⑤. Enzyme Induction or Inhibition

a.) Auto-induction:
- The drug increases its own metabolism over time.
- Enzyme levels increases with repeated dosing.

Example:
- Carbamazepine

b.) Enzyme Inhibition: Drug inhibits its own metabolism or that of other drugs.

Example: Ritonavir (Inhibits CYP3A4).

Result: Variable metabolism rates → non-linear kinetics.

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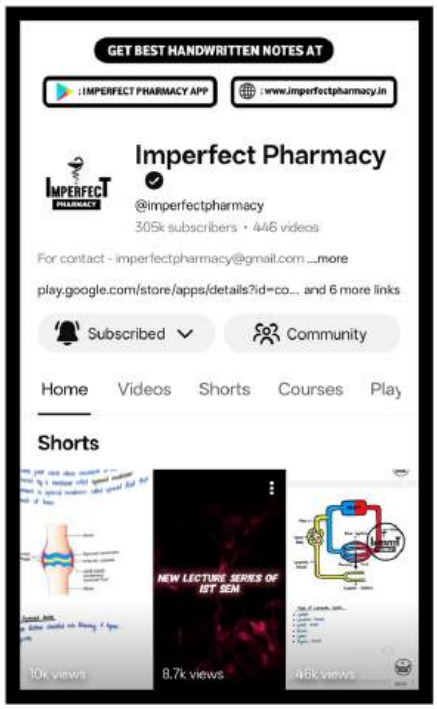

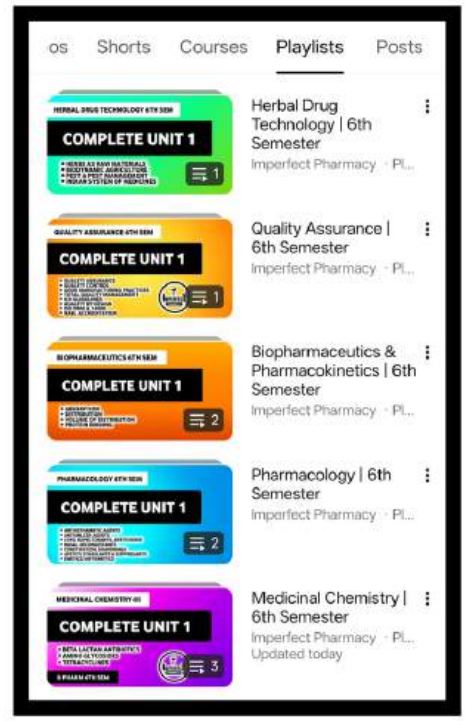

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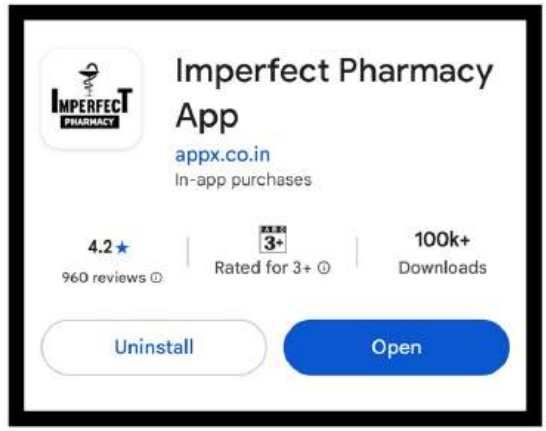

MICHAELIS MENTEN EQUATION

- The michaelis menten equation describes the rate of drug metabolism or elimination when metabolic pathways becomes saturated at higher drug concentrations.
- It is the fundamental equation used to characterize non-linear pharmacokinetics.
- It is expressed as:

$$-\frac{dc}{dt} = \frac{V_{max}\, C}{K_M + C}$$

Here, $-dc/dt$ = rate of change in drug concentration

V_{max} = Maximum elimination rate
K_M = Michaelis Menten Constant
C = Plasma Drug Concentration

Interpretation

There are 3 possible situation depending on values of K_M & C

1. $K_M = C$
2. $K_M >> C$
3. $K_M << C$

① $K_M = C$

- Under this situation, $-\frac{dc}{dt} = \frac{V_{max} C}{C+C} = \frac{V_{max} \ell}{2\ell}$

$$\text{Hence, } -\frac{dc}{dt} = \frac{V_{max}}{2}$$

- In this system is in a mixed order state - between first order & zero order.
- Any small dose increase states affecting elimination rate unpredictably.

② $K_M >> C$

- If $K_M >> C$, we can assume $K_M + C = K_M$

$$\text{Hence, } -\frac{dc}{dt} = \frac{V_{max} C}{K_M}$$

- Under this situation, system follows first order kinetics.
- The rate of elimination is proportional to drug concentration.
- If you doubt the close, the plasma concentration also roughly doubles.
- There is a linear relationship b/w close & response.

③ $K_M << C$

- Under this condition $K_M + C \approx C$

$$\text{Hence, } -\frac{dc}{dt} = \frac{V_{max}\, C}{C} = V_{max}$$

- In this system follows zero order kinetics.
- The rate of elimination becomes constant & independent of concentration.
- Increasing the dose further doesn't increase elimination rate.
- Toxicity can occur with small dose increases.

Example Of Drug Showing Non-Linear PK

Drug	Type Of Non Linearity	Reason
Phenytoin	Saturable metabolism	CYP enzyme saturation
Theophylline	Saturable metabolism	Hepatic enzyme saturation
Valproic acid	Saturable protein binding	Albumin saturation
Gabapentin	Saturable absorption	Active transport limited
Carbamazepine	Auto induction	Increases its own metabolism.

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