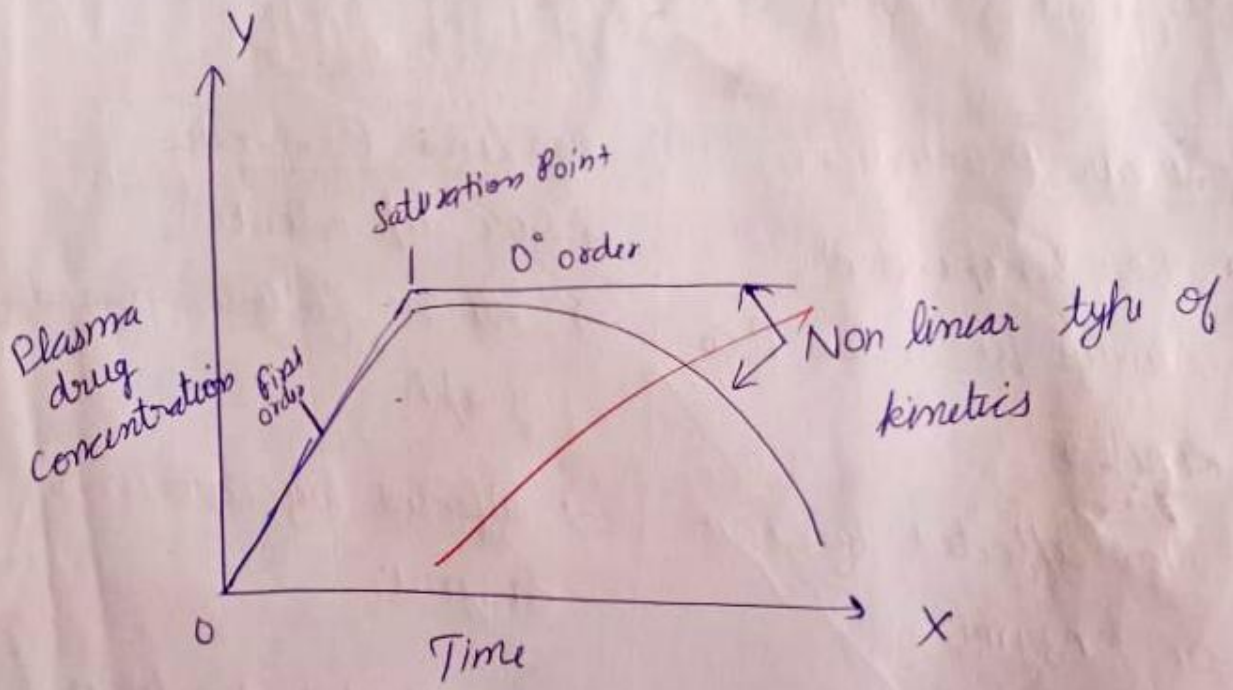
Non-linear Pharmacokinetics :-

When the Rate of absorption, distribution, elimination and metabolism is <u>not</u> directly proportional to the Drug concentration.

→ The Graph of Plasma drug concentration verses time in some drugs follow non linear pathway



→ Non linear follows <u>mixed pharmacokinetics</u> due to first and 0° order kinetic Pattern

☆ <u>Non linear Pharmacokenies</u> :- A dose dependent graph in when the concentration of drug dose, at some time the Rate of drug absorption increases, after

getting saturation point, the rate of drug concen... rate change is 0 or constant.

Factors Causing Non Linearity :-

⇒ Any condition when there is change in absorption, distribution, elimination and metabolism by different Pathologic or disease condition or presence of some different carrier or enzyme.

Linear P.Co Kinetics	Non Linear P.Co Kinetics
→ Dose Independent	→ Dose dependent
→ Always 1st order P.Co-Kinetics	→ It follows mixed graph.
→ Non affected by carrier or enzyme	→ affected by carrier or enzyme.
→ Non affected by disease or Pathological conditions	→ affected by disease or Pathological condition
→ Straigh lined graph	→ Non Straight lined graph

Test to detect Non-Linearity:-

→ to detect the cause of Non-Linearity.

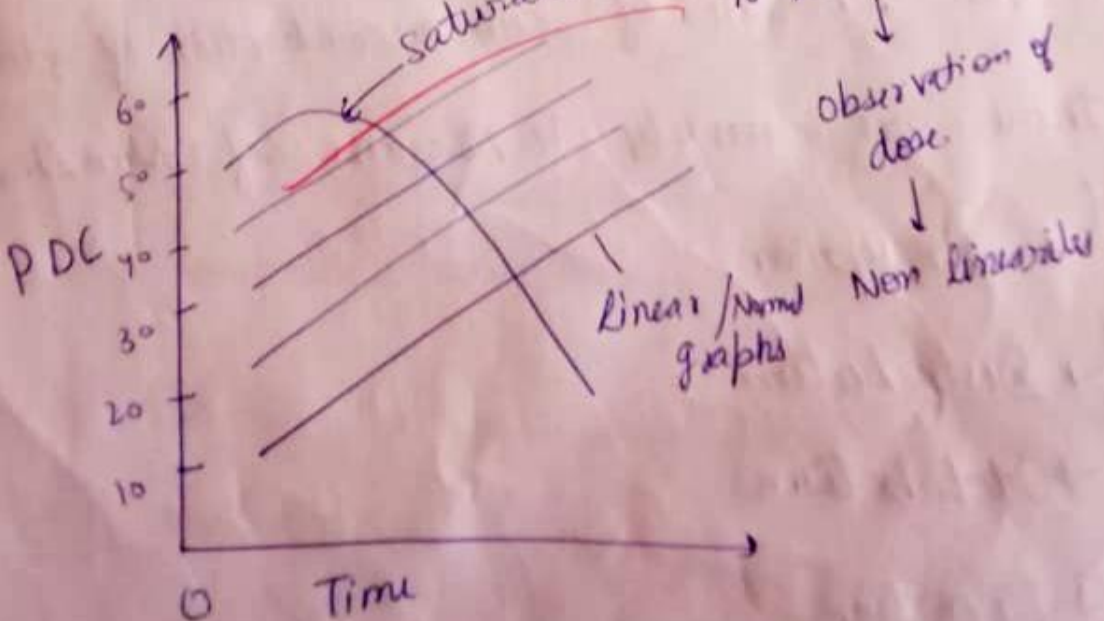
Methods

↳ Determination of Steady State Plasma concentration at different dose.

↳ Pharmacokinetic Parameter determination.

✱ Steady State PDC at diff. Doses:-

The diff. doses can performed on graph and detect the point at which the saturation or non-Linearity held and observe the dose.



✱ Determination of P kinetic Parameter:- The Parameter on graph on

Basis of Absorption, distribution, metabolism and elimination.

→ the factor can be observed at which the graph shows non-linearity and alteration in dose activity.

FACTORS CAUSING NON-LINEARITY

Some factors that cause decrease in effectiveness of drug or stop the effectiveness increasement on increase of concencentration of drug.

⇒ There are mainly 4 Reasons of Non Linearity

- Absorption
- Distribution
- Metabolism
- Excretion

Absorption of Drug -

First step of drug absorption P.cokinetic in which drug reach to systemic circulation. When 100% Not reached to Circulation then it cause non-linearity.

→ May due to
↳ Solubility and disolution of drug is limited
↓
Less solubility & dissolution cause low absorption.

exam- griseofulvin, Vitamins B_2 (Riboflavin), B_6 B_{12} (cyanocobalamin) absorbs through carriers show Non-linearity.

→ hepatic metabolism attain Saturation - Propanolol, hydrolazine, & Verapramil.
↓
Store in liver cause saturation

☆ **Drug distribution**:- drug reaches to receptors with help of Plasma Proteins unsaturation cause when there is no binding with Plasma Protein Or Saturation of Plasma

Protein and no empty receptors Present.

example → Phenylbutazone, naproxin.

↓

Saturation of Binding site on Plasma Protein

→ Saturation of Tissue binding site / Receptor

↓

exam - Thiopental Na., Fentanyl.

☆ Drug metabolism :- The unbinding of drug and Changing of Polarity of drug

→ Sometimes, liver can't metabolise the drug (at moderate)

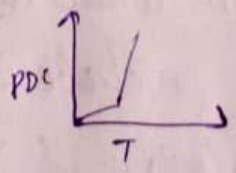
↓

exam, → Phenytoin, theophylline

→ enzyme Induction → Drug increase enzymes

↓

exam - Carbamazepine



☆ Drug Excretion :- After metabolism, drug eliminated from Body

→ Active tubular Secretion (Access)

↓

Shows Non-linearity

↓

exam - Penicillin

→ Active tubular reabsorption

↓

Exam- Water Soluble Vitamin (B, C) and glucose

☆☆☆☆

Michaelis Menten Equation

2 Scientists gave equation to find graph of a non-linear concentration Vs time of drug

→ given by Michaelis and Menden

$$-\frac{dC}{dt} = \frac{V_{max} \cdot C}{K_m + C}$$

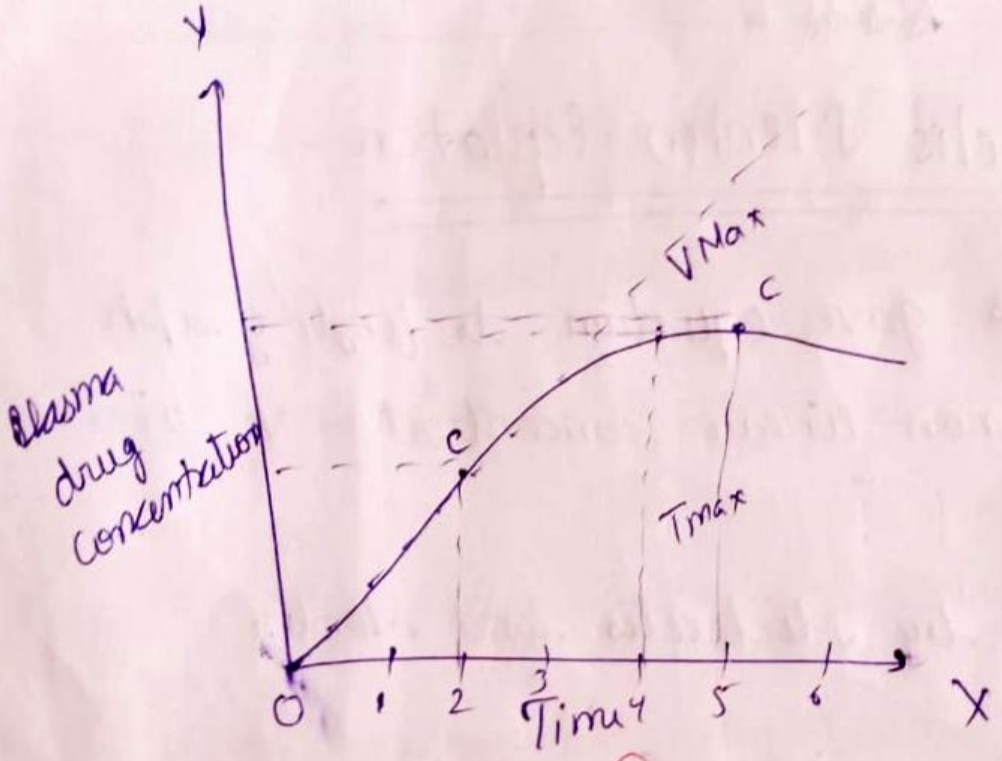
☆ $\frac{-dC}{dt}$ = Rate of concentration (P.cokinetic)

☆ V_{max} = Maximum concentration

☆ C = Concentration at any time

☆ K_m = michaelis menden constant

With the Equation, the concentration or rate of P. Kinetic can be found



$$-\frac{dC}{dt} = \frac{V_{max} \cdot C}{K_m + C}$$

→ $-\frac{dC}{dt}$ = Constant → C = Variable

→ Km = Variable Constant

☆ Case I - When Km = C

☆ Case II - When Km >>> C

☆ Case III - When Km <<< C

When Km = C

Let Km = C

Let $K_m = 1$, then also $C = 1$.

$$-\frac{dc}{dt} = \frac{V_{max} \cdot C}{K_m + C}$$

Put $K_m = 1$, $C = 1$

$$-\frac{dc}{dt} = \frac{V_{max} \times 1}{1+1}$$

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

→ V_{max} became half of Rate concentration when $K_m = C$.

When $K_m >> C$

If K_m Value is maximum than C, then C can suppose to be negligible.

$$\boxed{-\frac{dc}{dt} = \frac{V_{max} \cdot C}{K_m + C}}$$ original

$$\boxed{-\frac{dc}{dt} = \frac{V_{max}}{K_m}}$$ when $K_m >> C$

When $K_m << C$

If K_m is much smaller than C, so K_m can suppose to be negligible

$$-\frac{dc}{dt} = \frac{V_{max} \cdot C}{K_m + C}$$ Original

K_m = negligible

$$-\frac{dc}{dt} = \frac{V_{max} \cdot C}{C}$$

$$\downarrow$$

$$-\frac{dc}{dt} = V_{max}$$

then rate of concentration is proportional to time maximum have most Plasma drug concentration.

Estimation / Determination of K_m & V_{max}

Graph of IV Bolus Form Drug

↓

IV in form of Bolus

$$-\frac{dc}{dt} = \frac{V_{max} \cdot C}{K_m + C}$$

$$\log C = \log C_0 + (C_0 - C)\frac{V_{max}}{2.303 K_m}$$

$$Y = mx + C$$