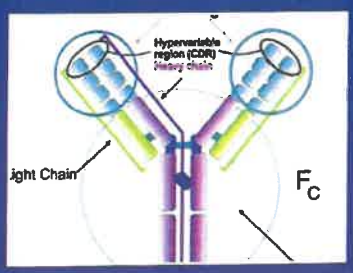
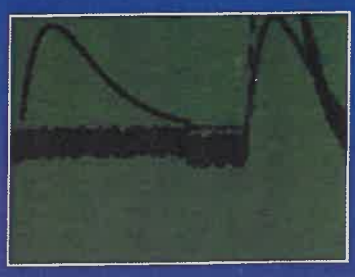
Cerebellum Pharmacology

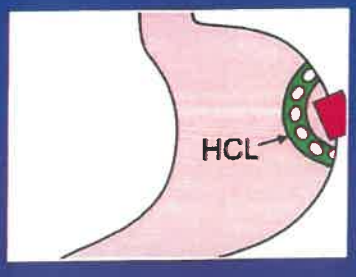
Cerebellum
Get the balance right

Cerebellum Pharmacology

For the Students
By the Teachers







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Section 1

General Pharmacology

1 CHAPTER

Introduction and Routes of Drug Administration

Pharmacology is the science dealing with drugs.

Two branches:

1. PharmacoKinetics → Effect of Body on Drug
2. PharmacoDynamics → Effect of Drug on Body

Drug:

Drug is a substance which is intended to be used to modify or explore the physiological function or pathological state for the benefits of recipient.

Risk benefit ratio:

If it is favorable, then drug is used e.g. Streptokinase is used in MI but not for peripheral vascular disease

Essential drugs

These are the drugs that cater to priority health care needs of a population.

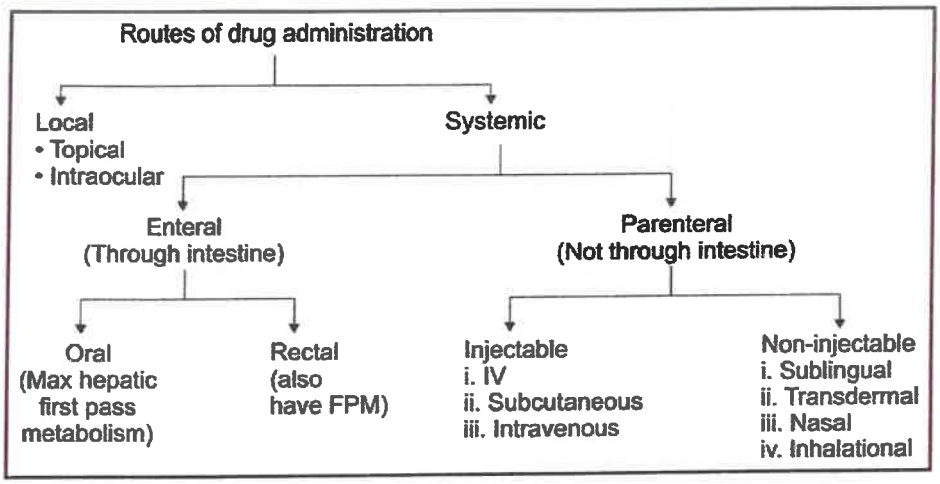
These drugs should be

- Always available
- In adequate quantity
- With assured quality

Mostly available as single compound.

Orphan drugs-

- These are drugs for which the expenditure done for the development of the drug is unlikely to be recovered from sale of the drug.
- Include drugs which are used for rare diseases.
- Also include drugs for relatively common diseases in third world; countries with less paying capacity



Route	Angle of needle with horizontal	Advantage
Intravenous	25°	Used in emergencies
Intramuscular	90°	-
Subcutaneous	45°	Self-administration possible
Intradermal	Almost 0°	For BCG and Allergy testing

- Intravenous route can be of two types:
  - Bolus
  - Infusion
- Because the drug is directly entering the systemic circulation, any volume of fluid can be given by itravenous route.
- Titration is possible by intravenous route
- Disadvantages of intravenous route are:
  - Sterile precautions should be followed
  - Require an expert person for administration
  - It is costly
- By Intramuscular route, maximum 5-10 ml volume can be given

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CHAPTER

Pharmacokinetics: Absorption

Pharmacokinetics

→ aka ADME Study

- Absorption
- Distribution
- Metabolism
- Excretion

Absorption

→ It is the movement of drug from site of administration to blood.

→ Lipid Solubility is the most important factor in absorption.

When The Medium Is Same, Then The Drug Will Cross

DRUG	MEDIUM	FORM	SOLUBILITY	CROSS
Acidic	Acidic	Non ionized	Lipid Soluble	✓
Basic	Basic	Non ionized	Lipid soluble	✓
Acidic	Basic	Ionized	Water Soluble	✗
Basic	Acidic	Ionized	Water Soluble	✗

Extra Edge

How much a drug will cross in different media?

e.g. Nature - Acidic

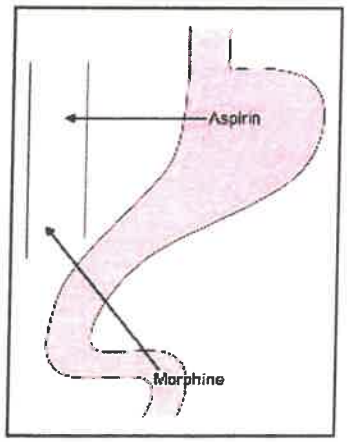
Pka = 6.0

pH	Lipid soluble	Water soluble
3.0	99.9%	0.1%
4.0	99%	1%
5.0	90%	10%
6.0	**50%**	**50%**
7.0	10%	90%
8.0	1%	99%
9.0	0.1%	99.9%

Henderson Hasselbach Equation

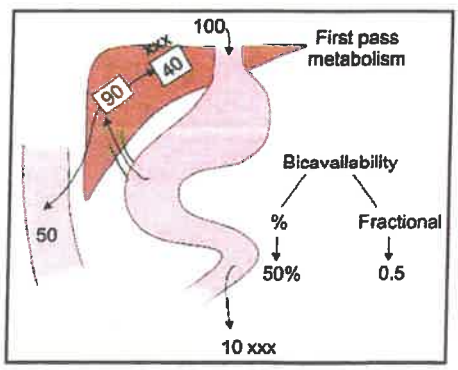
$$pH = pKa + \frac{[X^-]}{[HX]}$$

- Acidic Drug [Aspirin], mainly absorbed from stomach
- Basic Drug [Morphine] mainly absorbed from intestine



But practically all drugs (even acidic drugs like aspirin) are absorbed more from intestine as compared to stomach because:

- Large surface area of intestine
- Longer time drug stays in intestine



Bioavailability

→ It is the fraction of given dose which that reaches the systemic circulation in unchanged form

→ Bioavailability → Determines the Dose

High bioavailability → Low Dose

Low bioavailability → High dose

Factors affecting:

1. Absorption

↑ Absorption → ↑ Bioavailability

↓ Absorption → ↓ Bioavailability

2. Route of Administration

Route	% Bio-availability	Fractional Bio-availability
Oral	5-100	0.05 < F < 1
I.M.	75-100	0.75 < F < 1
S.C.	75-100	0.75 < F < 1
IV	100	1

3. First Pass metabolism/Pre systemic metabolism

↑ First Pass metabolism → ↓ Bioavailability

↓ First Pass metabolism → ↑ Bioavailability

NTG [Nitroglycerine]

- Has High First pass metabolism
- Sub Lingual Route is Preferred

Advantages of sublingual route

- Fast acting → Can be used in emergencies
- No First pass metabolism
- Self administration is possible
- After desirable action, we can spit/ingest the extra dose

How to calculate bioavailability?

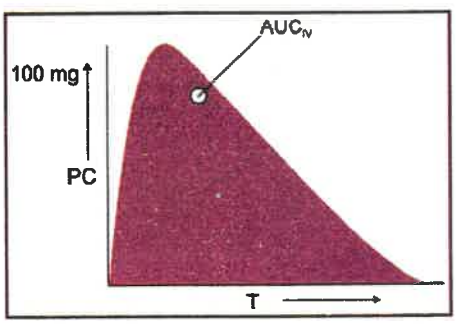
To know the bioavailability of Drug A by oral route

↓

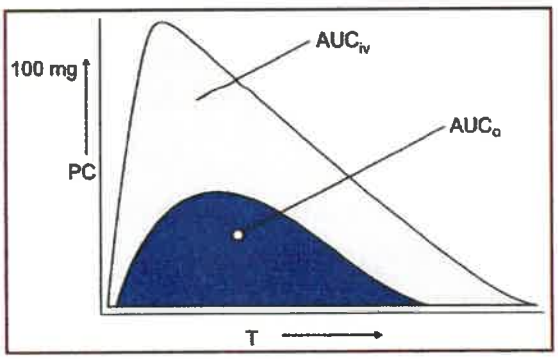
Give drug A 100 mg by IV route

↓

Then plot a graph



- Now same dose (100 mg) given orally and plot the same graph

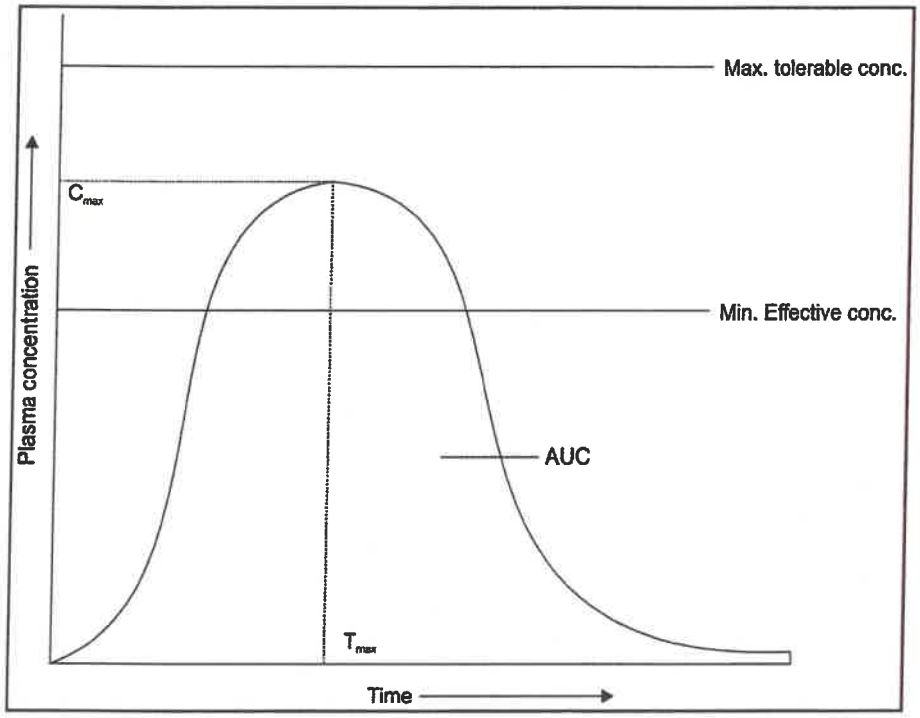


$$\text{Bioavailability} = \frac{\text{AUCo}}{\text{AUCiv}}$$

Bioequivalence (Biologically Equivalent)

- 2 brands of same drug are compared
  - If two brands of same drug have almost similar bioavailability (20%), these are called bioequivalent
  - Most of the drugs are bioequivalent except phenytoin

Plasma Concentration Vs Time Graph



C_{max}:	Maximum concentration obtained by a particular dose	Should lie between MTC and MEC
T_{max}:	Time in which plasma concentration becomes maximum	Tells Rate of absorption
AUC:	Total area covered by graph	Tells Extent of absorption

3 CHAPTER

Pharmacokinetics: Distribution

Distribution is a measure of amount of drug in tissues after absorption in the systemic circulation

Factors affecting:

1. Lipid Solubility

→ Most important Factor

Lipid soluble Drugs → Higher Distribution

Water Soluble Drugs → Lower Distribution

2. Plasma Protein Binding (PPB)

↑ PPB → Low Distribution

→ Acidic drugs bind to → Albumin

→ Basic drugs bind to → α1 Acid Glycoprotein

→ Different drugs have different percentage of binding

	Acidic drugs	Basic drugs
Examples	Aspirin Barbiturates Methotrexate	Atropine Morphine Amphetamine
Bind to	Albumin	α-1 acid Glycoprotein
Mnemonic	Salt with cations like Na^+ & K^+ e.g., Phenytoin sodium	• Drugs ending with 'INE' • Salts with anions like Ipratropium bromide

Extra Edge

Importance of PPB

a. Distribution:

→ if PPB is high, its volume of distribution (Vd) → ↓↓

b. Duration:

→ If drug has ↑ PPB Duration of action of drug ↑, because plasma protein to which it is bound serves as storage site.

c. Displacement interactions:

→ PPB sites on albumin & α1 - Acid glycoprotein arenon -specific

→ One drug may displace another drug leading to increase in free concentration of latter. This may result in toxicity.

→ For example, Warfarin is displaced by sulfonamides leading to bleeding.

d. Dialysis:

→ If a drug has ↑ PPB; dialysis of that drug cannot be done

→ Because proteins are not filtered during dialysis; thus the drug with ↑ PPB is retained along with plasma proteins

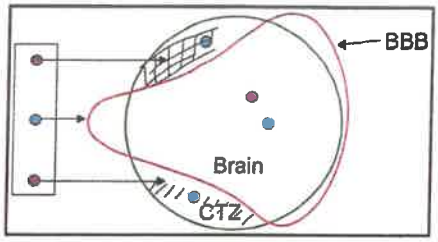
e. Filtration:

→ If, drug has ↑ PPB, its filtration would be lesser.

Cerebellum Academy

3. Barriers

- Brain is bound by Blood Brain Barrier.
- In circumventricular Organs, this barrier is absent.
- CTZ [chemoreceptor Trigger Zone] is important circumventricular organ.
- Vomiting not caused by → Anti-emetics and Anti-psychotics



Volume of Distribution (Vd)

$$\rightarrow Vd = \frac{\text{Amount given}}{Co}$$

→ Volume of Distribution Vd ∝ Amount of Drug in Tissues

More Vd → More distribution

Chloroquine

Drug with maximum Vd [> 1300 L]

Mostly distributed in Liver but site of preferred action is RBC

Loading Dose [LD]

Initial high dose given to start the action

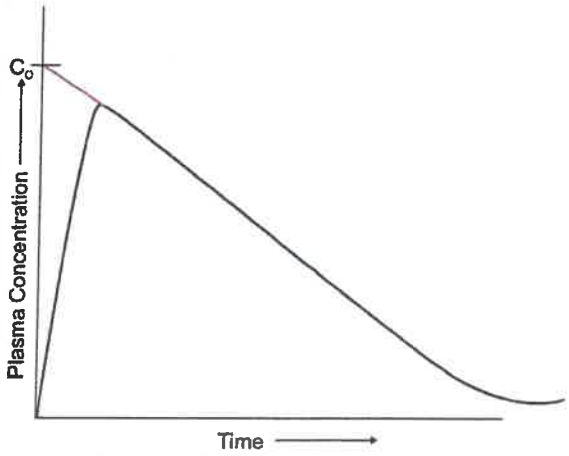
LD = Vd x Target Plasma Concentration

Maintenance Dose

Repeated doses given to maintain the plasma concentration.

MD = CL x Target PC

EXTRA EDGE



4 CHAPTER

Pharmacokinetics: Metabolism

Elimination

→ Termination of action of Drug → ELIMINATION

→ Includes Metabolism and Excretion

Metabolism (Biotransformation)

Fate of Metabolism

1. Active	→	Inactive
2. Active	→	Active
DIAZEPAM	→	OXAZEPAM
3. Inactive [PRODRUG]	→	Active
LEVODOPA	→	DOPAMINE

Prodrugs:

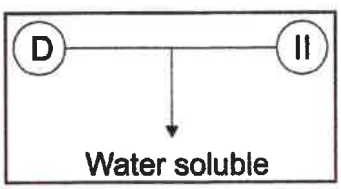
All	- ACE inhibitors (PRIL) except captopril and isinopril
Prefer	- PPI's (Prazole), Prednisone
Doing	- Dipivefrine
M	- Methyldopa, Minoxidil, 6-MP
D	- levo-Dopa
In	- Irinotecan
Clinical	- Clopidogrel, Carbimazole
Subjects	- Sulfasalazine, Sulindac

Aim of Metabolism → To Make a Drug Water Soluble (Polar)

PHASE I REACTIONS	PHASE II REACTIONS
→ Mostly catabolic Reactions	→ Mostly anabolic reactions
→ Includes – Oxidation (MC Phase I reaction) – Reduction – Hydrolysis – Cyclization – Deamination	→ Includes – Glucuronide [MC Phase II Reaction] conjugation – Glutathione conjugation – Acetylation – Methylation – Sulfate conjugation

Purpose of Phase I → Expose the Functional Group on the drug

Purpose of Phase II → Makes the drug water soluble



Enzymes

→ Divided into Microsomal and Non-microsomal

Microsomal	Non-microsomal
– Present in smooth endoplasmic reticulum	– Present outside SER
– Can be induced or inhibited	– Cannot be induced or inhibited
– Most Phase I reactions and glucuronidation	– Most Phase II reactions

→ Enzyme inhibitors (e.g., erythromycin) decrease the metabolism of drugs metabolized by microsomal enzymes (e.g., theophylline). This increases their plasma concentration and thus can lead to toxicity.

→ Enzyme inducers (like rifampicin) increase the metabolism of drugs metabolized by microsomal enzymes (e.g., warfarin). This reduces plasma concentration and thus action of these drugs. We should increase the dose of warfarin when rifampicin is given concurrently.

Enzyme Inducers		Enzyme inhibitors	
G	Griseofulvin	Vit	Valproate
P	Phenytoin	K	Ketoconazole
R	Rifampicin	Can't	Cimetidine
S	Smoking	Cause	Ciprofloxacin
Cell	Carbamazepine	Enzyme	Erythromycin
Phone	Phenobarbitone	Inhibition	Isoniazid

→ Most of antiepileptics are Enzyme Inducers except Valproate

→ Most of antibiotics are Enzyme Inhibitors except Rifampicin and Griseofulvin

Cytochrome p450 Enzymes

These are one type of microsomal enzymes.

P → Stands for pigment

450 → This pigment absorbs maximum light at wavelength 450 nm

Nomenclature:

e.g.: CYP-3A4

3→ Family

A → Subfamily

4 → Isoform

Most of the drugs are metabolized by CYP3A4 followed by CYP2D6

Drugs metabolized by 3 A4 (CT SCAN)

C Cyclosporine

T Tacrolimus

S Statins

C CAT Drugs — Cisapride, Astemizole

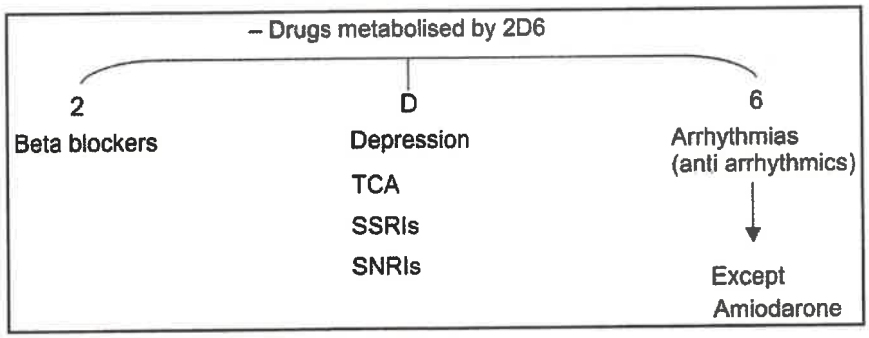
A Amiodarone — Terfenadine

-These are withdrawn from market becasuse these cause QT prolongation in ECG

N Navirs (HIV protease inhibitors)

Drugs metabolized by 2C9

- Clotting (Warfarin) [C means clotting]
- Phenytoin [Mirror image of 9 looks like P of Phenytoin]



Drugs metabolised by 2C19

- Clopidogrel
- Ticlopidine

Therefore, PPIs are avoided with clopidogrel

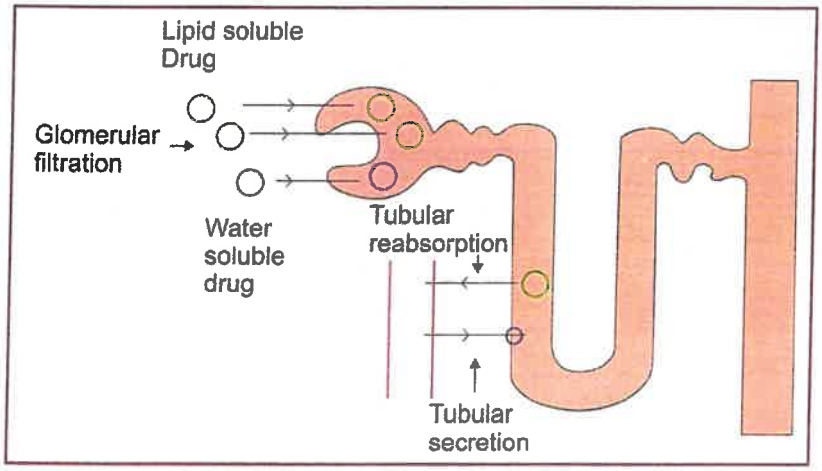
5

CHAPTER

Pharmacokinetics: Excretion

→ Most of the drugs are excreted through kidney

→ Some of the drugs are excreted through sweat (e.g., Lithium)



Glomerular Filtration

→ Lipid soluble as well as water soluble drugs can befiltered

→ Filtration is inversely proportional to Plasma Protein binding

Tubular Reabsorption

→ 99% of GFR is reabsorbed

- Lipid soluble drugs reabsorbed
- Water soluble drugs excreted

Weak Acidic drug poisoning	Weak basic drug poisoning
(Aspirin, Barbiturates, Methotrexate)	(Amphetamine)
↓	↓
Urine is made alkaline by giving $NaHCO_3$	Urine is made acidic by giving NH_4Cl
↓	↓
Acidic drugs gets ionized (water soluble/polar)	Basic drugs gets ionized
↓	↓
No tubular reabsorption	No tubular reabsorption
↓	↓
Drug is excreted out	Drug is excreted out

Tubular Secretion

→ Due to pumps/transporters in proximal tubules

→ The drug is secreted from blood into urine through these transporters

a) Organic anion transporter

b) Organic cation transporter

→ These transporters are Saturable (One drug can be transported at one time)

Clinical Importance

- Penicillin is short acting (Due to rapid tubular secretion)
- Penicillin + Probenecid → Long acting
- Probenecid has higher affinity for transporters and Prevents Penicillin secretion
- It makes penicillins long acting.

Extra Edge

If

CL > GF	Tubular secretion must be present
CL < GF	Tubular reabsorption must be present

Order of Kinetics

Rate of elimination $(\text{Plasma concentration})^{\text{order}}$

- In First order Kinetics - Rate of elimination α plasma concentration
- Zero order Kinetics - Rate of elimination is constant
- Second order Kinetics - Rate of elimination α $(\text{plasma concentration})^2$
- Third order Kinetics - Rate of elimination α $(\text{plasma concentration})^3$

First order kinetics	Zero order kinetics
→ Fraction is constant	→ Amount is constant
R α PC	R = Constant
CL = Constant	CL α 1/PC
t½ = Constant	t½ α PC

- Majority of drugs follow First Order Kinetics
- **Drugs Following Zero Order Kinetics are**
  - Zero → Zero order Kinetics
  - W → Warfarin
  - A → Alcohol/Aspirin
  - T → Theophylline
  - T → Tolbutamide
  - Power → Phenytoin

Reason

→ Order of Kinetics depends on Enzyme Saturation

- If enzymes are abundant → Follow 1st order Kinetics
- If enzymes are limiting factor → Follow Zero Order Kinetics.

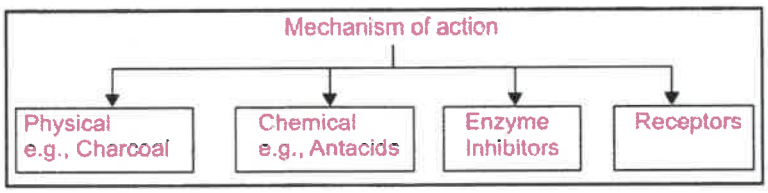
Zero order Kinetics is also known as Pseudo-Zero order kinetics/Non-Linear Kinetics

7

CHAPTER

Pharmacodynamics: Introduction and Enzyme Inhibitors

Pharmacodynamics deals with effect of a drug on the body.



Enzyme inhibition

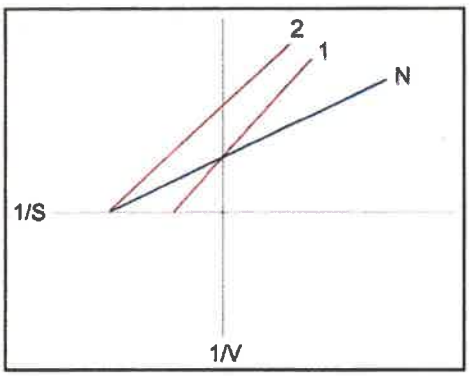
Competitive - Drug competes with substrate by binding to active site of enzyme.

Noncompetitive - Drug binds to allosteric site of enzyme.

Property	Competitive Inhibition	Non-Competitive Inhibition
Structure	Same as substrate	Different
Binding site	Active	Allosteric site
Reversibility	Surmountable	Unsurmountable
Km	Increases	Do not change
Vmax	Do not change	Decreases

Lineweaver Burke Plot:

- Also known as double reciprocal plot
- Graph between 1/S (on X-axis) and 1/V (on Y-axis)
- X-axis tells K_m and Y-axis tells V_{max}
- If lines intersect at X-axis, it is non-competitive inhibition
- If lines intersect at Y-axis, it is competitive inhibition



(N) Is Normal graph

(1) Is competitive inhibitor

(2) Is non-competitive inhibitor