Enzyme Inhibition

A substance which **binds with the enzyme** cause a **decrease in catalytic** activity of that enzyme is called **enzyme inhibitor**.

There are three broad categories of enzyme inhibition

1. **Reversible inhibition.**
2. **Irreversible inhibition.**
3. **Allosteric inhibition.**

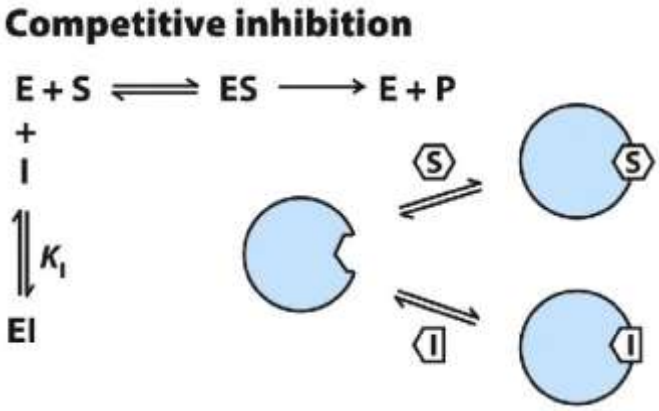
Reversible inhibition

The inhibitor binds **non-covalently** with enzyme and the enzyme inhibition **can be reversed** if the inhibitor is removed.

A. Competitive inhibition
B. Non-competitive inhibition
C. Uncompetitive inhibition
D. Mixed inhibition

A. Competitive inhibition

- A competitive inhibitor **competes with the substrate** for the active site of an enzyme.
- **Closely resembles** the real substrate (S) is regarded as a substrate **analogue**.
- Inhibitor occupies the **active site** it prevents binding of the substrate to the enzyme.
- The inhibitor **competes with substrate** and **binds at the active site** of the enzyme but does not undergo any catalysis.
- During the reaction, ES and EI complexes are formed as shown below



- The inhibition could be overcome by a high substrate concentration.

- In competitive inhibition, the **Km value increases** whereas **Vmax remains unchanged.**

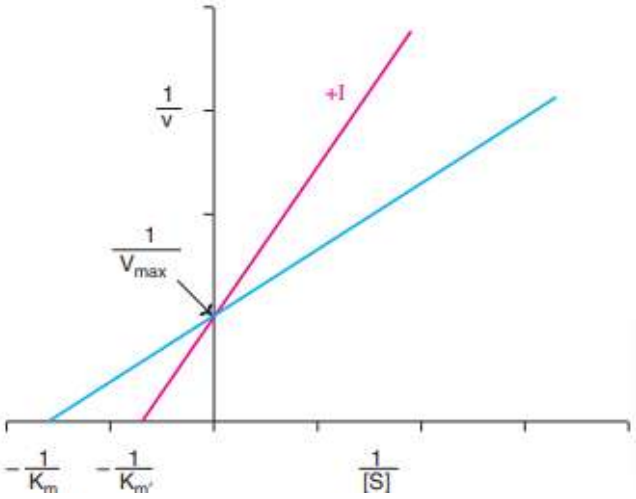


Fig Effect of competitive inhibitor on enzyme velocity. Lineweaver-Burk plot (Red lines with inhibitor; competitive inhibitor increases Km, unalters Vmax).

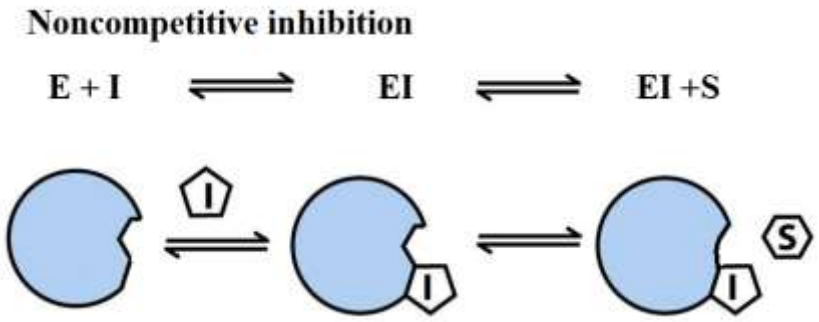
Examples of competitive inhibitors

1. Enzyme - *Succinate dehydrogenase*
   Substrate – *Succinic Acid*,
   Inhibitor - *malonic acid, glutaric acid and oxalic acid*.
2. Enzyme - *Alcohol dehydrogenase (ADH)*
   Substrate – *Ethanol*
   Inhibitor – *Methanol*
3. Enzyme - *Xanthine oxidase*
   Substrate – *Hypoxanthine*
   Inhibitor – *Allopurinol*

B. Non-competitive inhibition

- The inhibitor do not bind to the active site but **attaches itself to another part of the enzyme** called **allosteric site**. The binding of the inhibitor to the allosteric site changes the overall shape of the active site, so that it does not fit to the normal substrate and **slows or prevents** the reaction taking place.
- This type of inhibition **decreases the turnover rate of an enzyme** rather than interfering with the amount of substrate binding to the enzyme. The reaction is **slowed rather than stopped**.

- The overall relation in non-competitive inhibition is represented below.



- For non-competitive inhibition, the **Km value is unchanged** while **Vmax is lowered**.

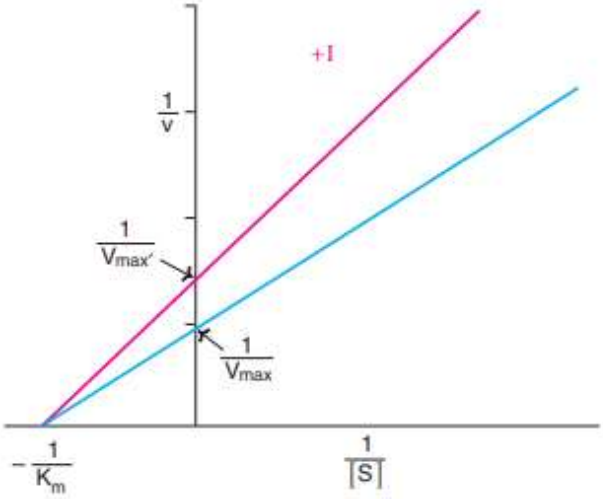


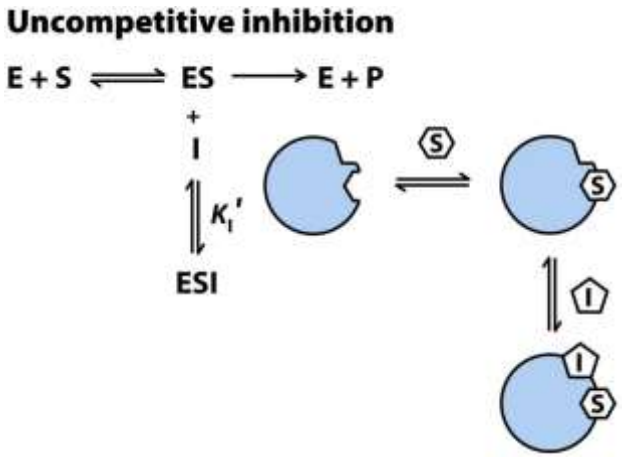
Fig: Lineweaver-Burk plot (Red lines with inhibitor, non-competitive inhibitor does not change Km but decreases Vmax).

Example

The increased concentration of **isoleucine** during its synthesis from threonine, it binds **threonine deaminase** non-competitively and bring about a decrease in the process of isoleucine synthesis.

C. Uncompetitive Inhibition

- An uncompetitive inhibitor **binds at a site distinct** from the substrate active site and, unlike a competitive inhibitor, binds only to the **ES complex**. The overall relation in uncompetitive inhibition is represented below



- For uncompetitive inhibition, both the **Km and Vmax value is lowered**.

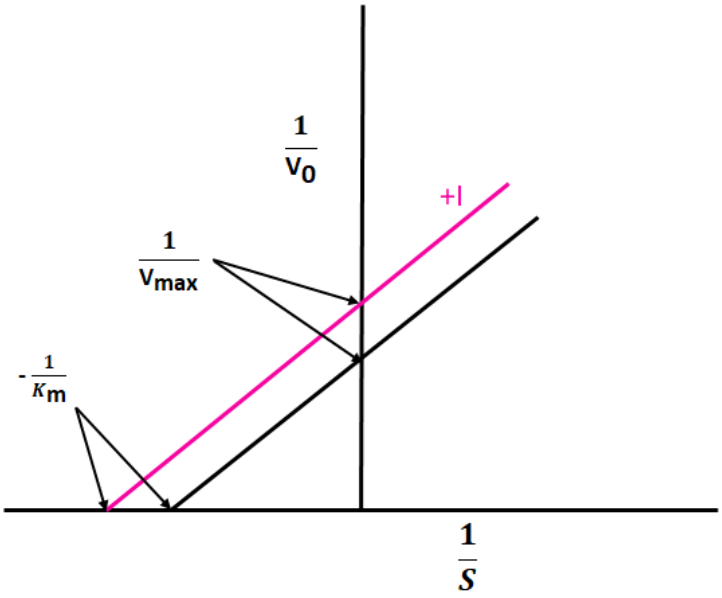
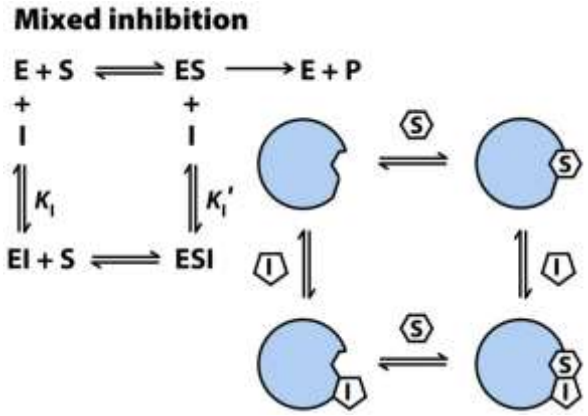


Fig: Lineweaver-Burk plot (uncompetitive inhibitor lowered both the Km and Vmax value).

D. Mixed Inhibition

- A mixed inhibitor also **binds at a site distinct** from the substrate active site, but it binds to **either E or ES.**
- However, the binding of inhibitor can affect the binding of substrate by **changing the conformation of the enzyme**. This type of inhibition can be reduced but not eliminated by increasing concentration of substrates.

- The overall relation in mixed inhibition is represented below



- A mixed inhibitor usually affects **both Km and Vmax**.

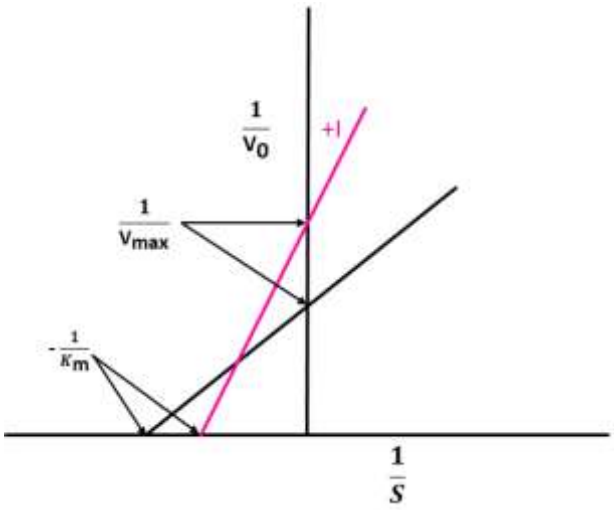


Fig Lineweaver-Burk plot (mixed inhibitor increase the Km and lower the Vmax value).

Irreversible inhibition

- The inhibitors bind **covalently** with the enzymes and inactivate them, which is irreversible.
- Iodoacetate combines with sulfhydryl (SH) groups at the active site of these enzymes like **papain** and **glyceraldehyde 3-phosphate dehydrogenase** and makes them inactive.

- The **penicillin** antibiotics act as irreversible inhibitors of **serine – containing enzymes**, and block the bacterial cell wall synthesis.
- **Cyanide** inhibits **cytochrome oxidase** (binds to iron atom) of **electron transport chain**. Fluoride inhibits enolase (by removing manganese), and thus glycolysis.

Suicide inhibition

- Suicide inhibition is a specialized form of irreversible inhibition. In this case, the **original inhibitor** (the structural analogue/competitive inhibitor) is converted to a more **potent** form by the same enzyme that ought to be inhibited.
- Allopurinol gets converted into alloxanthine which is a more effective inhibitor of xanthine oxidase.
- 5-fluorouracil gets converted to fluorodeoxyuridylate which inhibits the enzyme thymidylate synthase, and thus nucleotide synthesis.