Lec5 5th stage

Organic Pharmaceutical Chemistry IV

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Assist prof. Dr.Rita Sabah Elias
College of Pharmacy, university of Basrah

Drug delivery approaches (Chemical delivery system)

Targeted delivery of drugs

Drug targeting:- is the delivery of drugs to receptors (or) organs (or) any other specific part of the body. The targeted delivery of drugs may be achieved by different approaches, mainly classified into 3 categories.

1. Physical (or) Mechanical approach.
2. Biological approach.
3. Chemical approach

Physical (or) Mechanical approach.:-It involves formulation of drug using a particulate delivery device, which will allow differential release of the drug (as microspheres, nanoparticles, liposomes,etc.,)

Biological approach:- It involves the delivery of drugs using carrier system with targeting moiety, Such as :-

1. Antibodies directed against specific cell surface antigens.
2. Endogenous carbohydrate-binding proteins (lectins)
3. Low molecular weight protein for renal targeting(lysozyme).
4. Hormones functioning as specific ligands for receptors on specific targets.

Chemical approach:-

1. **Prodrug approaches→Chemical drug delivery system (CDS)**

2. **Retro metabolic approaches→Soft drug approaches**

Chemical drug delivery systems

Prodrug approaches:- **Prodrug reaches the target site and that the enzymatic or chemical process exists at the target site for conversion of the prodrug to the active drug.**

Advantages of chemical delivery system:-

1) prodrug reach the site of action in high concentration.
2) High levels of metabolism (chemically or enzymatically) at target site.
3) Limit side effects and increase effectiveness.

Factor that control or success of this approach:-

1- Extend of target organ perfusion.
2- Rate of conversion of prodrug to the active drug in both target and non target site.
3- Input / output rates of prodrug and drug from the target site.

Example on target site

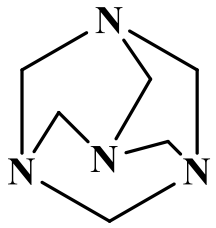
1) Cancer cells (anticancer)
2) Kidney and urinary tract (Renal disease).
3) GIT disease.
4) Viral material.
5) Ocular tissue (eye).
6) Blood brain barrier (CNS disease).
7) Bacterial cells.

The basic goal of drug delivery system

1) Protect the drug from non specific biological environment.
2) Protect a non specific biological environment from the drug to achieve some site specific delivery system.
3) Site specific drug delivery has been evaluated extensively for drug with narrow therapeutic windows such as anticancer.

Examples

Antibacterial agent (Methenamine)



Methenamine
treatment UTI

Low pH

Kidny

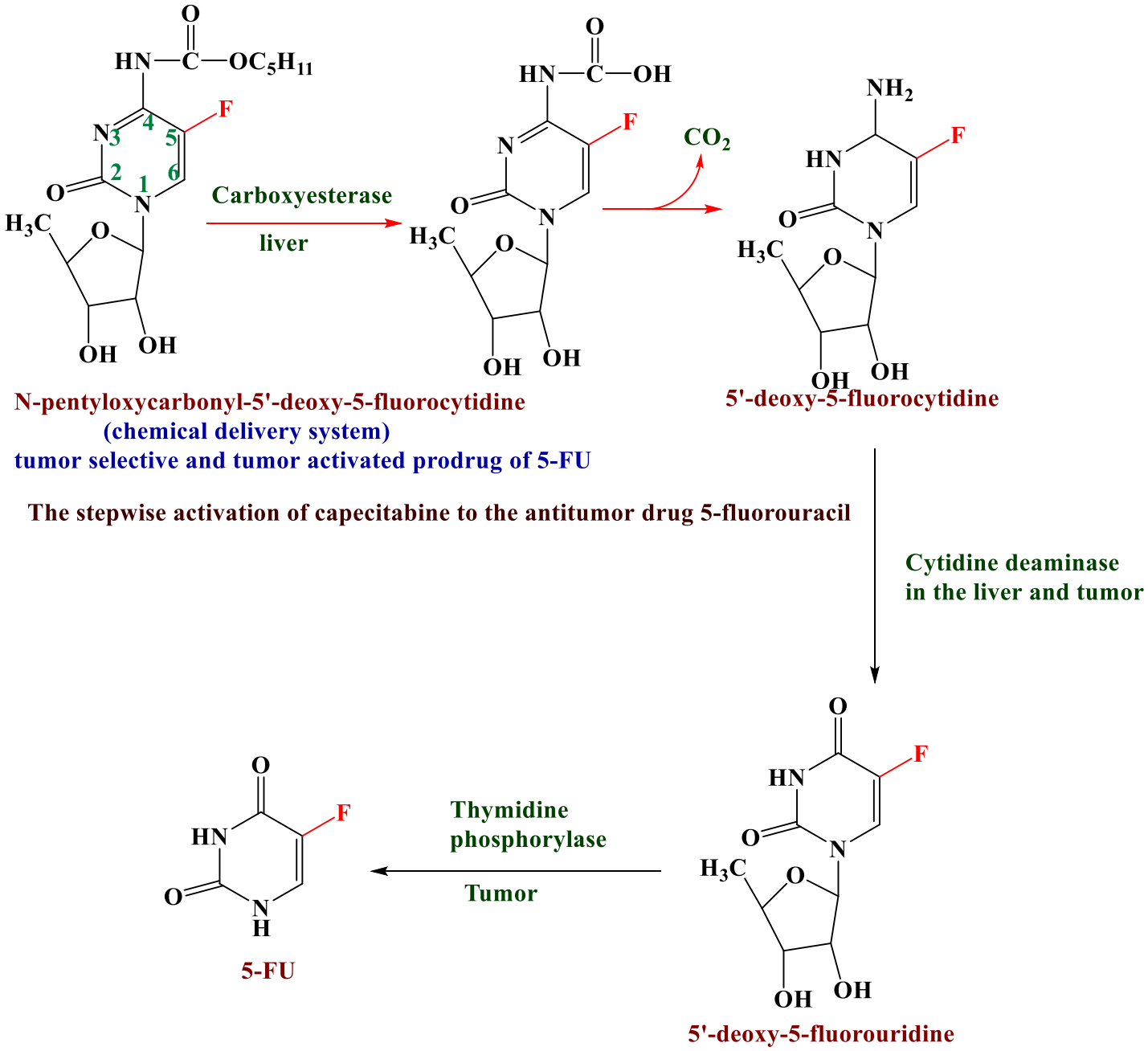
$6CH_2=O$ + $4\ NH_3$

Methenamine is a site-specific Chemical delivery system for the urinary tract antiseptic agent formaldehyde. The low pH of the urine promotes the hydrolysis of the prodrug methenamine
to formaldehyde (the active antibacterial agent). The rate of hydrolysis increases with increased acidity (decreased pH), and this can be promoted by administration of urinary pH-lowering agents or by diet. The pH of the plasma is buffered to about 7.4, and the rate of hydrolysis is low, preventing systemic toxicity from formaldehyde. As mentioned above, this compound is administered in enteric coated tablets that prevent dissolution and, therefore, premature hydrolysis in the highly acidic environment of the stomach.

b. Antitumor agent (Capecitabine)

A number of prodrugs for cancer chemotherapy have been designed for selective delivery of active drug to tumor tissue, based on [1)] higher levels of activating enzyme in the tumor cell than in normal tissue.[2)] Many enzymatic systems show higher activity in tumor cells than in normal tissue because of the higher growth rates associated with tumor tissue. Peptidases and proteolytic enzymes are among those systems showing higher activity in and near tumor cells.

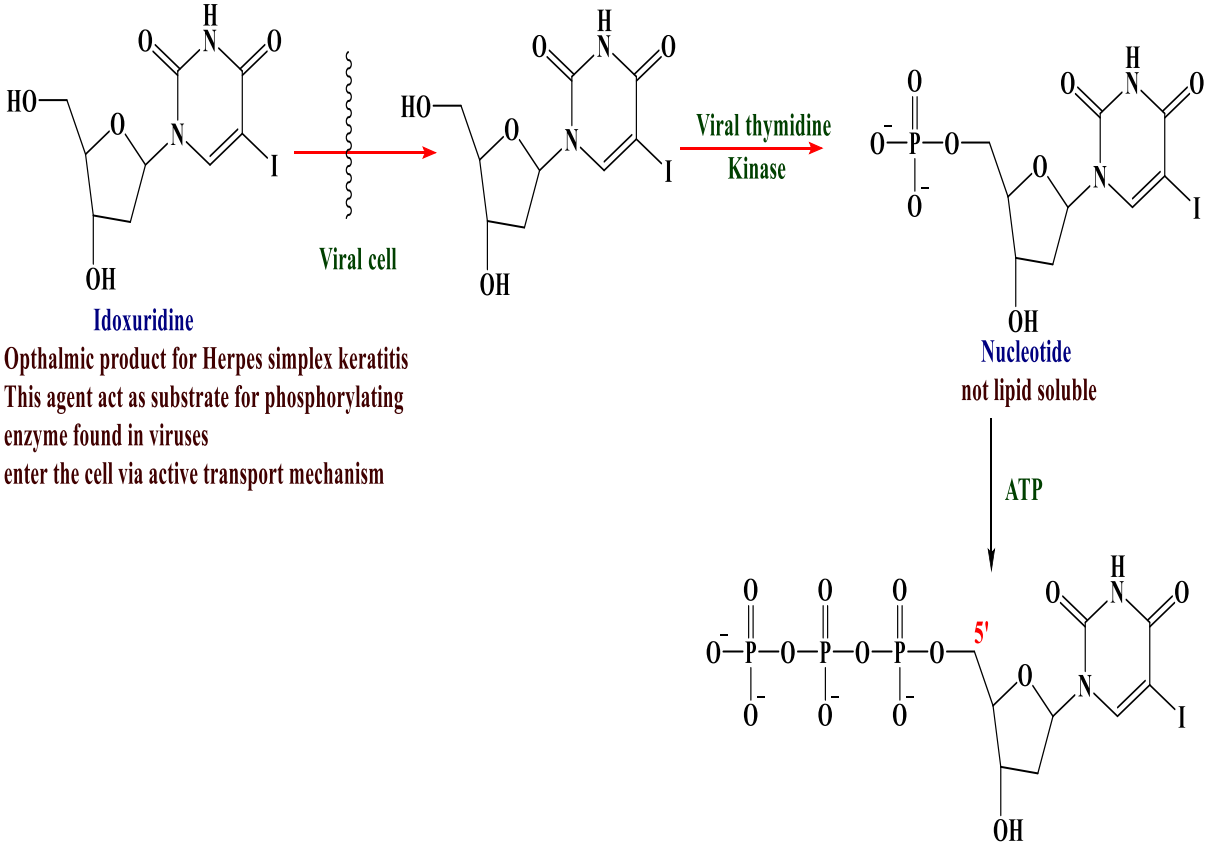
Capecitabine is well absorbed orally and undergoes three activation steps resulting in high tumor concentrations of the active drug. It is first hydrolyzed by liver carboxylesterase, the resulting metabolite being a carbamic acid which spontaneously decarboxylates to 5-deoxy-5-fluorocytidine. The enzyme cytidine deaminase, which is present in the liver and tumors, then transforms 5-deoxy-5-fluorocytidine into 5-deoxy-5-fluorouridine. Transformation into 5-FU is catalyzed by thymidine phosphorylase and occurs selectively in tumor cells.


Carboxyesterase
liver
CO_2
N-pentyloxycarbonyl-5'-deoxy-5-fluorocytidine
(chemical delivery system)
tumor selective and tumor activated prodrug of 5-FU
5'-deoxy-5-fluorocytidine
The stepwise activation of capecitabine to the antitumor drug 5-fluorouracil
Cytidine deaminase
in the liver and tumor
Thymidine
phosphorylase
Tumor
5-FU
5'-deoxy-5-fluorouridine

b. Antiviral agent (Idoxuridine)

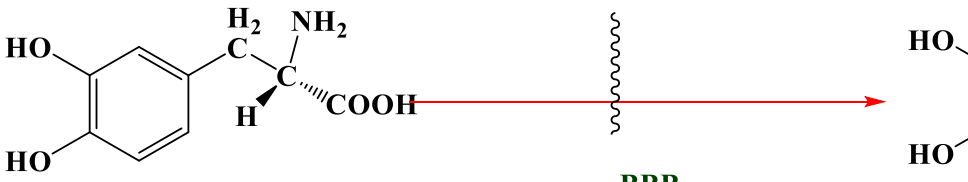
These drugs serve as substrates for phosphorylating enzymes found in viruses, and the phosphorylated species is the active antiviral agent. The active phosphorylated species is incorporated into viral DNA, disrupting viral replication and, thus, producing the antiviral effect. These drugs do not undergo phosphorylation by mammalian cells, so the prodrug is specific for those sites where it serves as a substrate for phosphorylation enzymes. One of the requirements

for site-specific chemical delivery was the proper input/output ratios for prodrug and active drug species at the target. The relative physicochemical properties of prodrug and its phosphorylated derivative suggest an appropriate input/output ratio for site specificity. The prodrug can readily penetrate the virus, and the increased polarity of the phosphorylated derivative would serve to retain that active species inside the virus. The combination of increased polarity and viral retention of the active phosphorylated species likely reduces any human toxicity that might be associated with this active species.



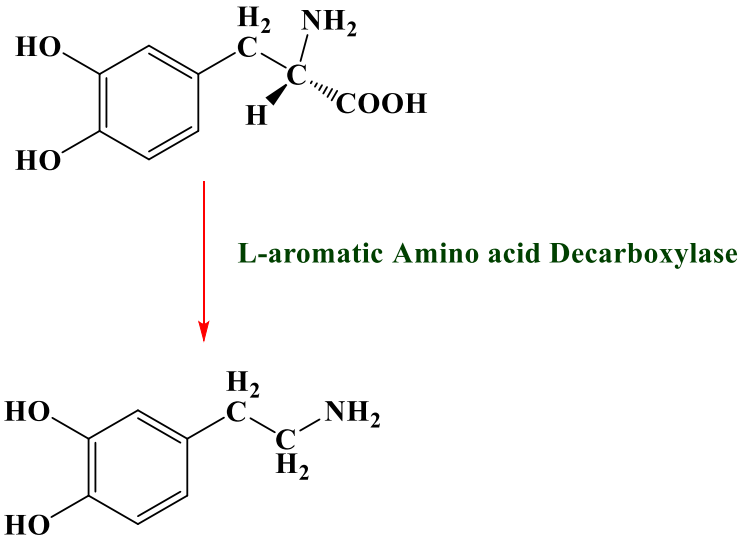
Q/ Explain Input/output ratios for prodrug and active drug species at the target site.

4- BBB cells [a]{L-Dopa or Levodopa (antiparkinsonism • agent)}



L-dopa

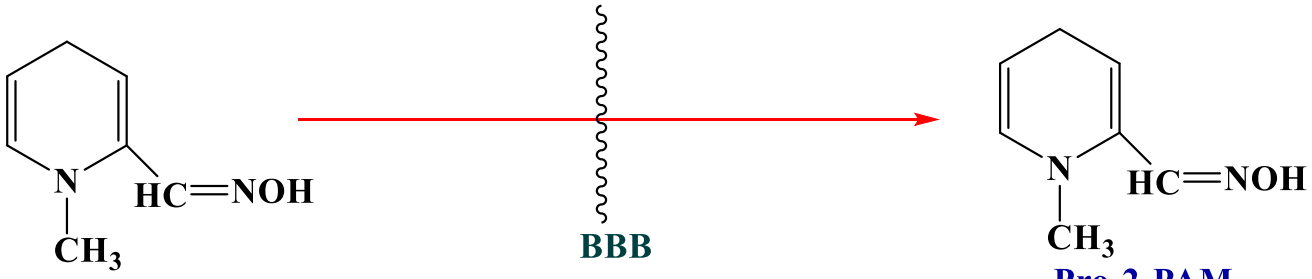
The amino acid drug L-dopa can be considered a site specific chemical delivery system that delivers the drug dopamine to the brain. The brain has an active transport system that operates to incorporate L amino acids into the central nervous system (CNS), and L-dopa is transported into the brain in this manner. Once across the Blood-brain barrier. L-dopa undergoes decarboxylation to yield the active metabolite, dopamine.



Dopamine

Direct systemic administration of Dopamine does not produce Significant levels of the drug in the brain because of its high polarity and poor membrane permeability as well as its facile metabolic degradation by oxidative deamination.

b) **Pro 2-PAM** is the prodrug form of 2-PAM, an important antidote for the phosphate and carbamate acetylcholinesterase inhibitors used in insecticides and nerve gases.



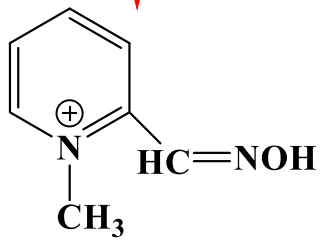
Pro-2-PAM

is a dihydropyridine derivative that undergoes metabolic and chemical oxidation to yield the active drug 2-PAM

The nonionic pro-2-PAM can easily cross the blood—brain barrier, and oxidation to 2-PAM within the brain essentially traps the active cationic drug species inside the brain.

Pro-2-PAM

Oxidation



2-PAM

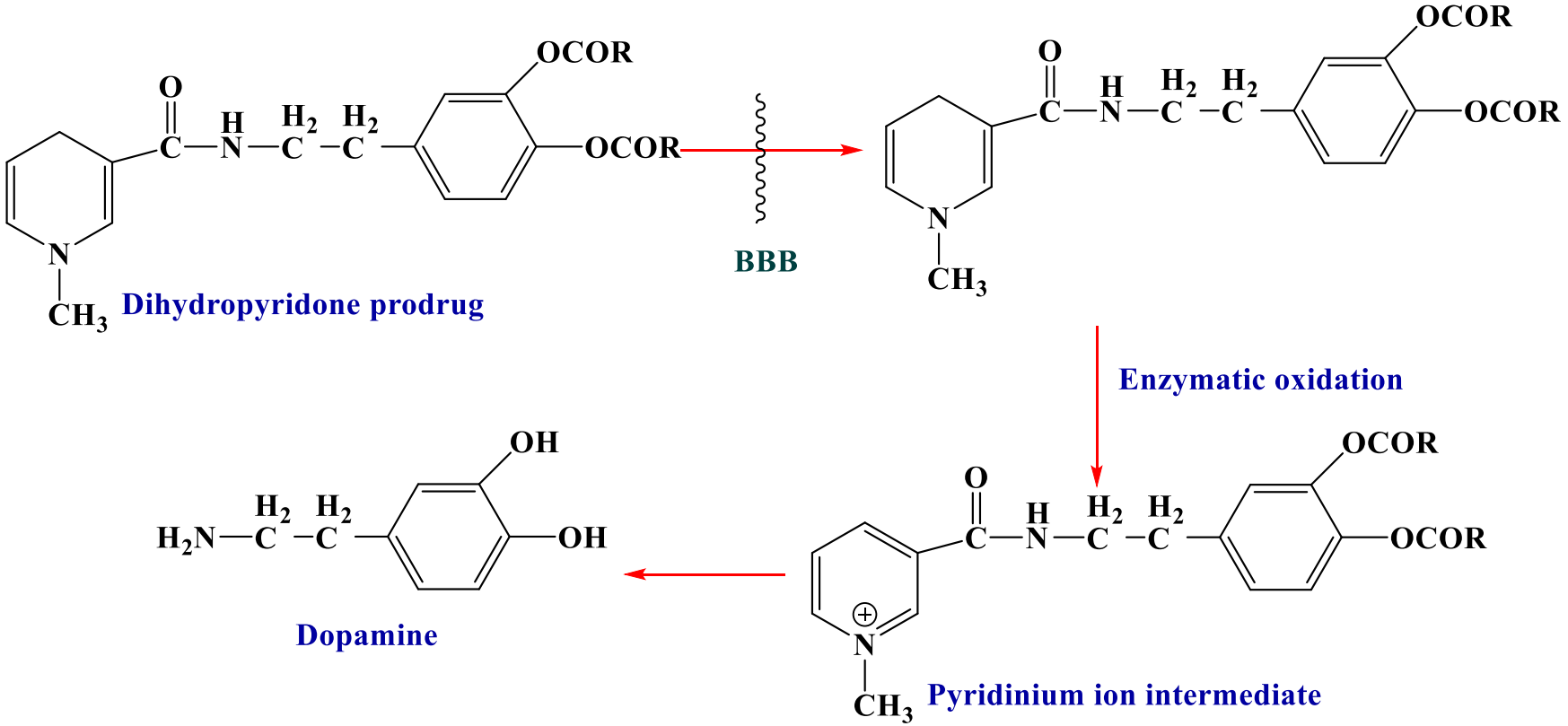
the polar properties of 2-PAM because the presence of cationic species, prevent this drug from being absorbed following oral administration and restrict the drug from access to the brain, even after IV administration

C) Dihdropyridine -prodrug of dopamine

The delivery of drugs across the blood—brain barrier has been a significant issue in the design of many therapeutic compounds. Only very lipophilic drugs can cross into the brain without the aid of some active uptake process, such as the one that operates to incorporate essential amino acids into the CNS. The facile oxidation of the **dihydropyridine** ring system has been extensively investigated as a general process for chemical delivery of a number of drugs to the CNS.

This process is a multistep procedure involving delivery of the drug—dihydropyridine derivative to the brain via facile diffusion across the blood—brain barrier, followed by oxidation to the quaternary pyridine cation, which is trapped in the brain. The drug is then released from

the pyridine cation by a second metabolic/chemical event.

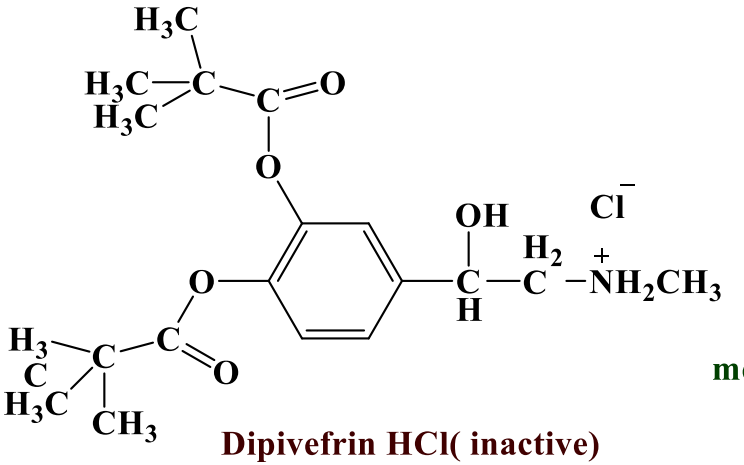


Dihydropyridine - based drug delivery system for dopamine

4. Human eye (Dipivefrin)

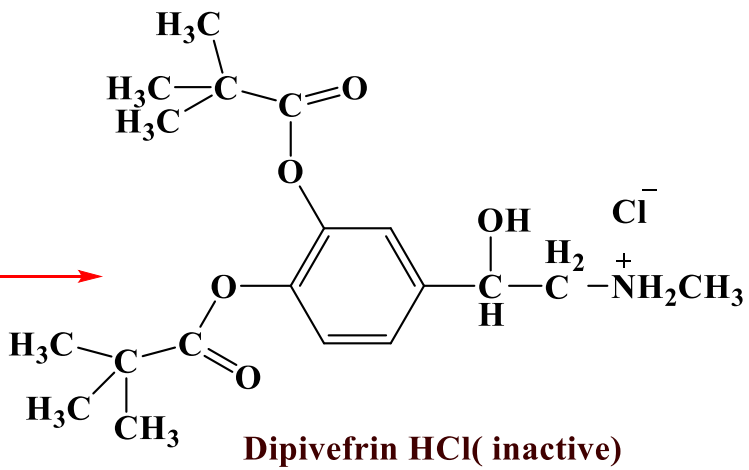
Lipophilic esters of epinephrine, such as the dipivaloyl ester of epinephrine show better corneal penetration following direct application to the eye than the more polar parent drug epinephrine.

The esterases necessary for the hydrolysis of the prodrug are readily available in the eye and skin. The more polar drug species, epinephrine is then localized within the lipophilic membrane barriers of the eye, and the drug remains available at the target site to produce its antiglaucoma effect.



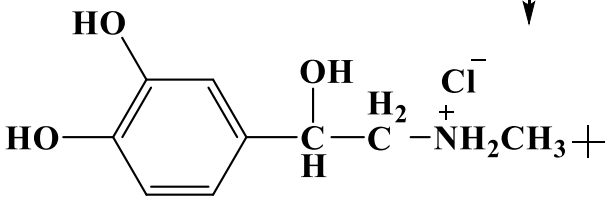
Dipivefrin HCl(inactive)

membran barrier of eye

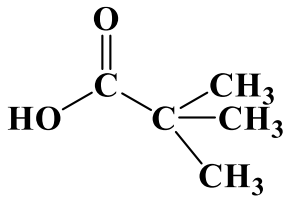


Dipivefrin HCl(inactive)

Esterase



Epinephrine

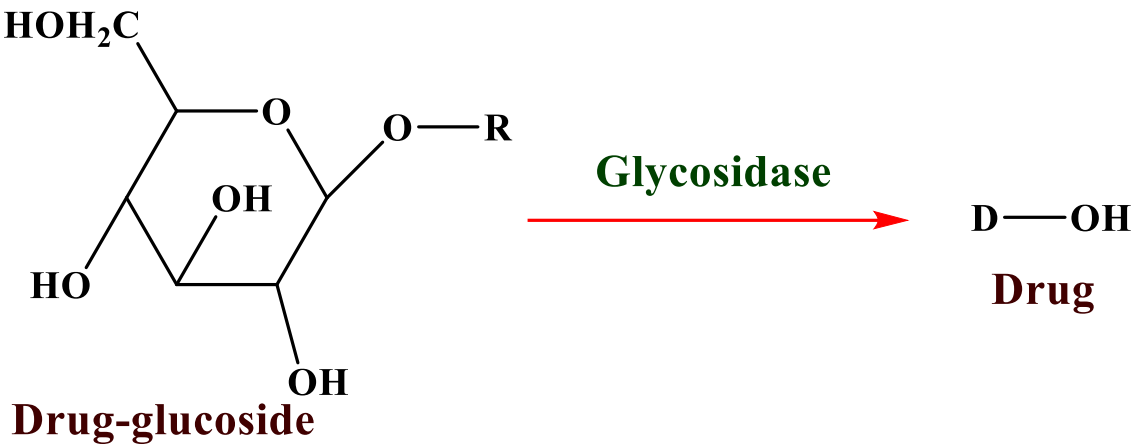


Pivalic acid

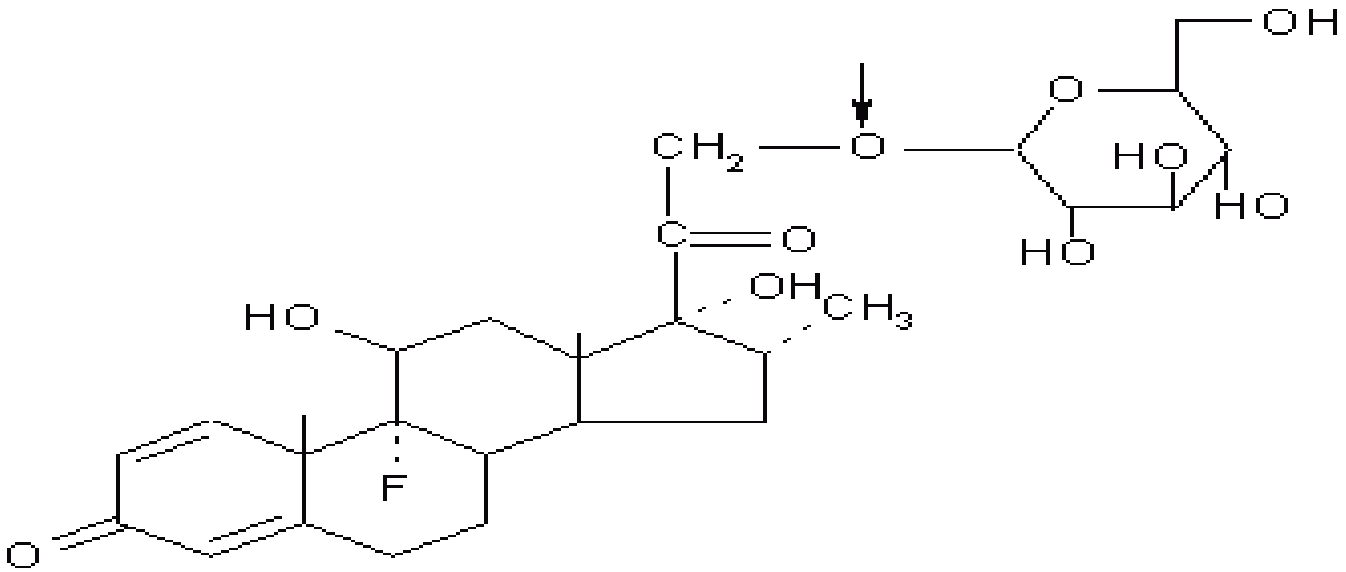
4. Colon and lower GI tract

The delivery of drugs to the **colon** and **lower GI tract** has taken advantage of the unique enzymatic processes found in colon bacteria. The glycosidase activity of these bacteria allows hydrolysis of glycoside derivatives of drugs in the colon and provides higher concentrations of active drug.

A number of **steroid** drugs demonstrate increased effectiveness in the lower GI tract following administration as their glycoside derivatives. The polar glycoside derivatives of the steroids are not well absorbed into the bloodstream from the GI tract and remain available to serve as substrates for the bacteria that are found primarily in the human colon.



Activation of drug -glucoside by bacterial glycosidase



Dexamethasone-21-β-D-glucoside
(Arrow shows site of action of glycosidase)