BASIC CONCEPTS AND APPLICATION OF PRODRUG DESIGN

Introduction

- Almost all drugs possess some undesirable physicochemical and biological properties.
- Drug candidates are often discontinued due to issues of poor pharmacokinetic properties or high toxicities
- Their therapeutic efficacy can be improved by eliminating the

undesirable properties while retaining the desirable ones.

- This can be achieved through biological, physical or chemical means.

- The **Biological approach** is to alter the route of administration which may or may not be acceptable to patient.

- The **Physical approach** is to modify the design of dosage form such as controlled drug delivery of drug.

- The best approach in enhancing drug selectivity while minimizing toxicity, is the **chemical approach** for design of prodrugs.

Definition

- The term prodrug relates to "***Biologically inert derivatives of drug molecules that undergo an enzymatic and/or chemical conversion in vivo to release the pharmacologically active parent drug.***"

- A prodrug is a chemically modified inert drug precursor, which upon biotransformation liberates the pharmacologically active parent compound.

History of Prodrugs

- The first compound fulfilling the classical criteria of a prodrug was **acetanilide**, introduced into the medical practice by Cahn and Hepp in 1867 as an antipyretic agent. Acetanilide is hydroxylated to biologically active **acetaminophen**.

- Another historical prodrug is **Aspirin** (acetylsalicylic acid), synthesized in 1897 by Felix Hoffman (Bayer, Germany), and introduced into medicine by Dreser in 1899.

- The prodrug concept was intentionally used for the first time by the Parke-Davis company for modification of **chloramphenicol** structure in order to improve the antibiotic's bitter taste and poor solubility in water. Two prodrug forms of chloramphenicol were synthesized: **chloramphenicol sodium succinate** with a good water solubility, and c**hloramphenicol palmitate** used in the form of suspension in children.

Objectives of Prodrug Design

- There are three basic, overlapping objectives in prodrug research:

1. **<u>Pharmaceutical Objectives</u>:**

- To improve solubility, chemical stability, and organoleptic properties

- To decrease irritation and/or pain after local administration,

- To reduce problems related with the pharmaceutical technology of the active agent.

2. Pharmacokinetic Objectives:

- To improve absorption (oral and by non-oral routes).
- To decrease presystemic metabolism to improve time profile.
- To increase organ/ tissue-selective delivery of the active agent.

3. Pharmacodynamic Objectives:

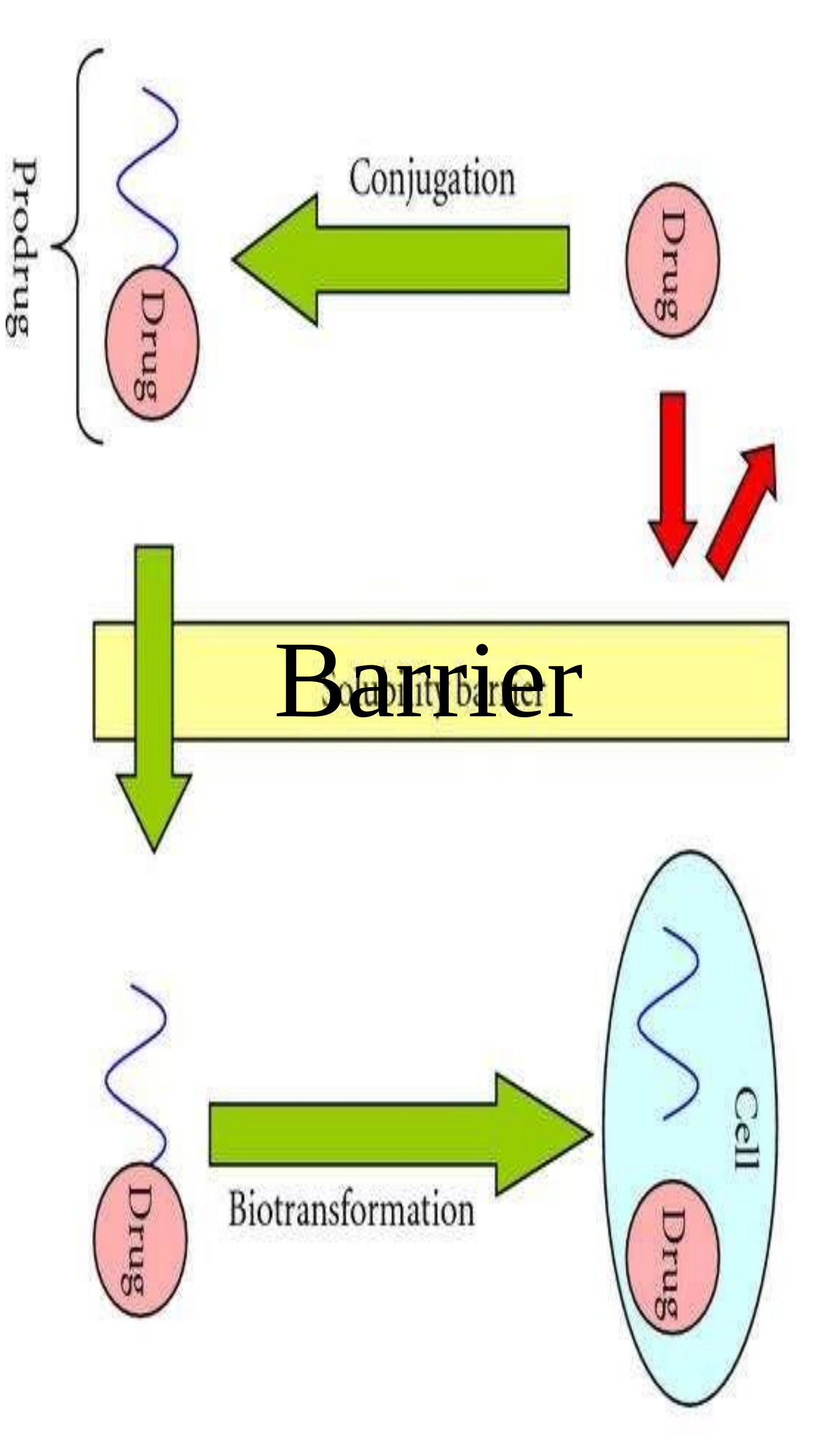
- To decrease toxicity and improve therapeutic index.
- To design single chemical entities combining two drugs (co-drugs strategy.

Prodrug concept

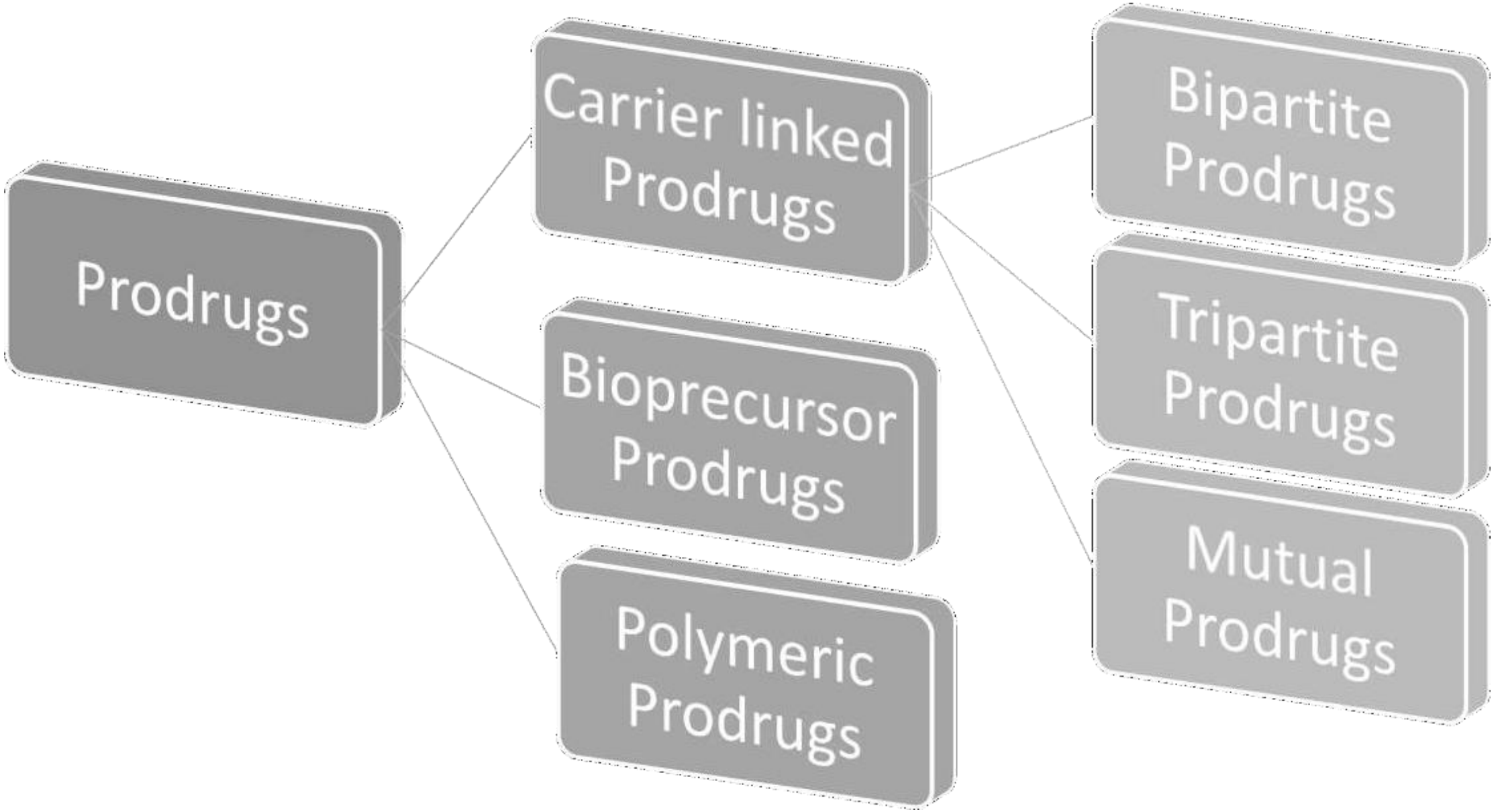
- The awareness that the onset, intensity and duration of drug action are greatly affected by the physicochemical properties of drug has promoted the emergence of various prodrugs.

- Most of the limitations can be overcame by prodrug approach, but after overcoming the various barriers, the prodrug should rapidly convert into active moiety after reaching the target site.

- The design of an efficient, stable, safe, acceptable and aesthetic way to target a drug to its site of action while overcoming various physical, chemical and social barriers is certainly the utilization of the prodrug approach holds great potential.


Prodrug
Drug
Conjugation
Drug
Barrier
Drug
Biotransformation
Cell
Drug

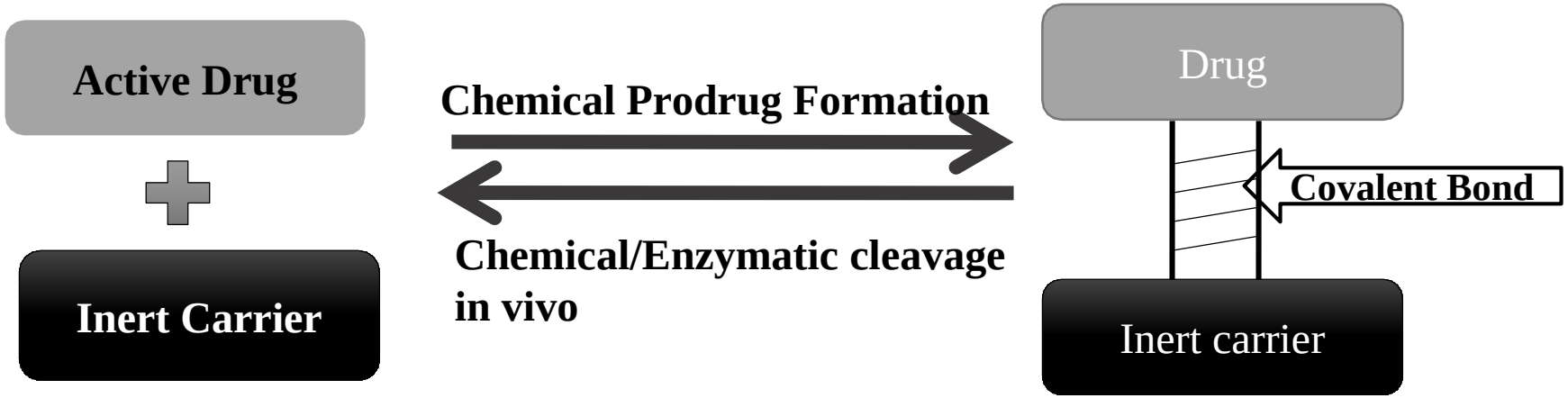
Classification of Prodrugs



Carrier linked prodrug

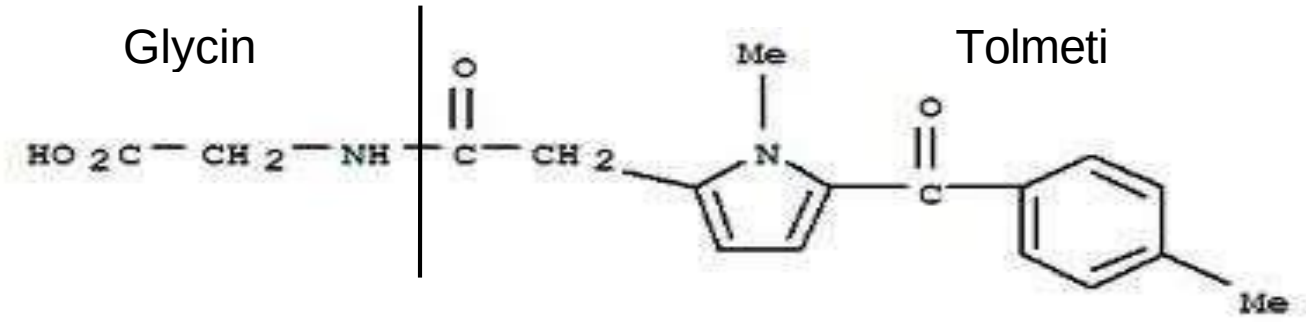
- Carrier linked prodrug consists of the attachment of a carrier group to the active drug to alter its physicochemical properties.

- The subsequent enzymatic or non-enzymatic mechanism releases the active drug moiety.

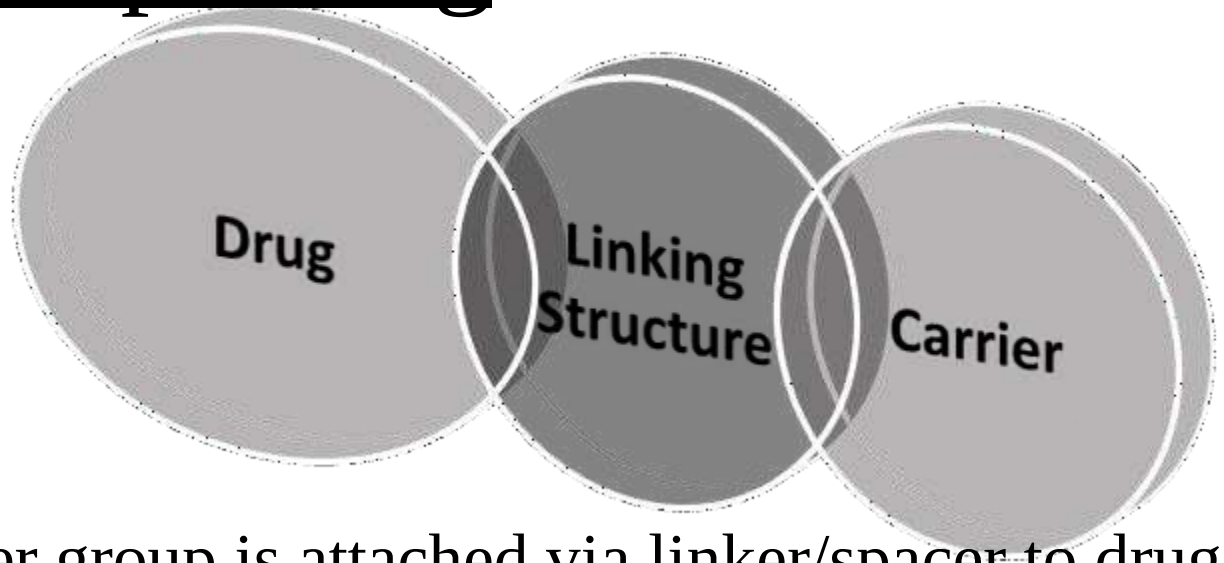


Bipartite prodrug

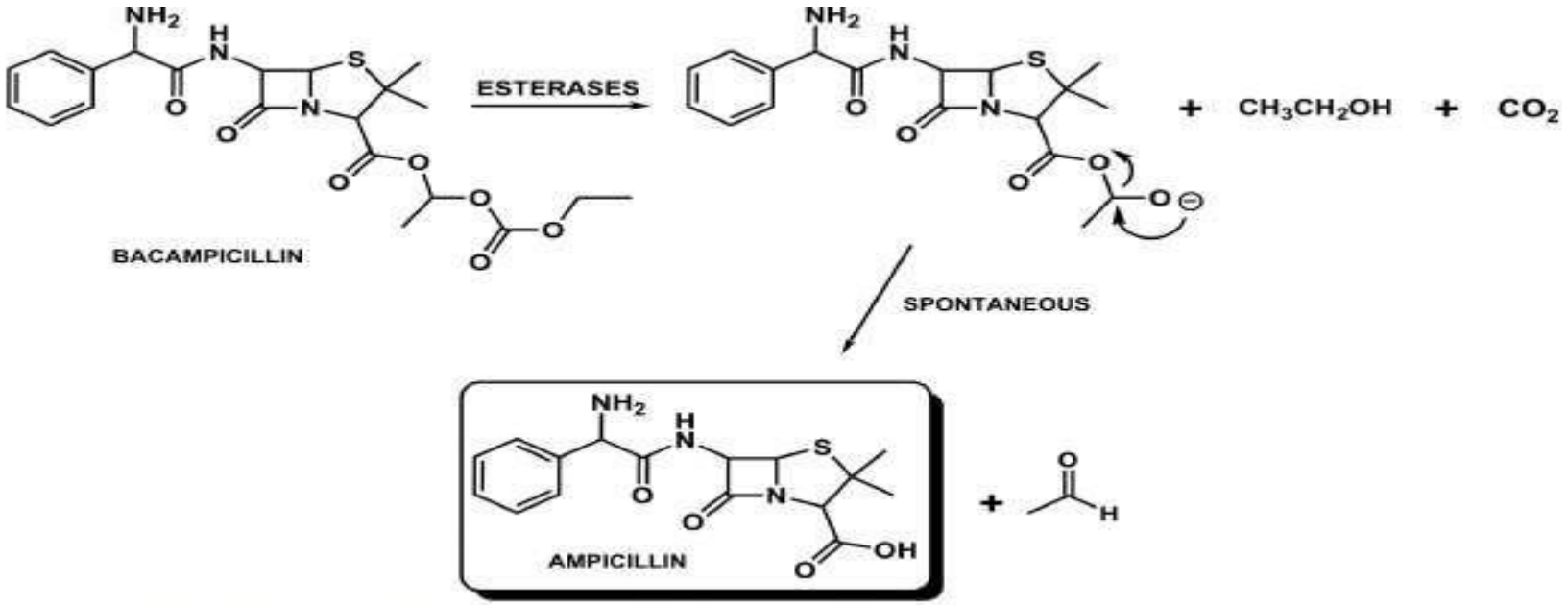
- It is composed of one carrier (group) attached to the drugs.
- Such prodrugs have greatly modified lipophilicity due to the attached carrier. The active drug is released by hydrolytic cleavage either chemically or enzymatically.
- E.g. Tolmetin-glycine prodrug.



Tripartite prodrug

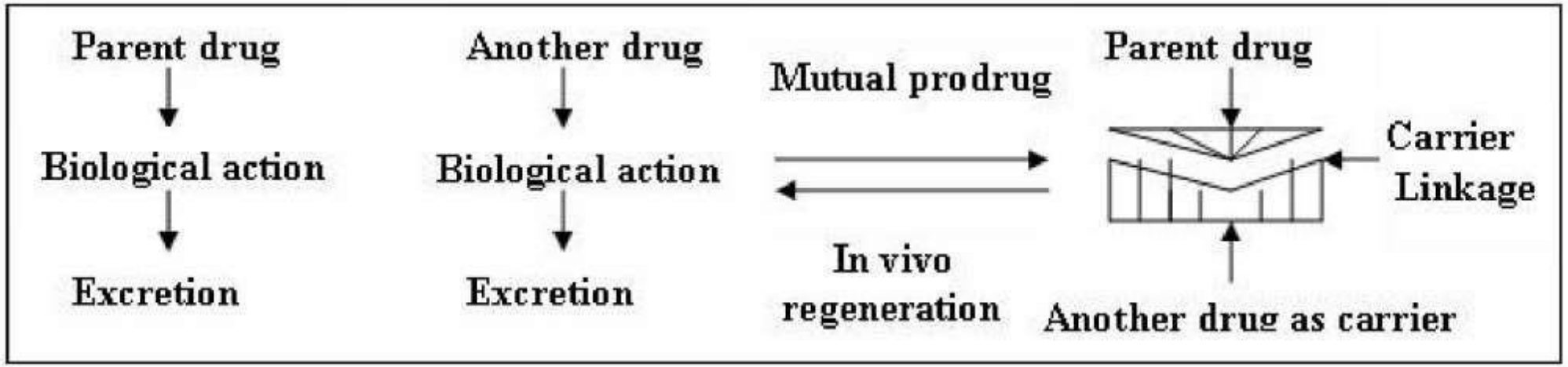


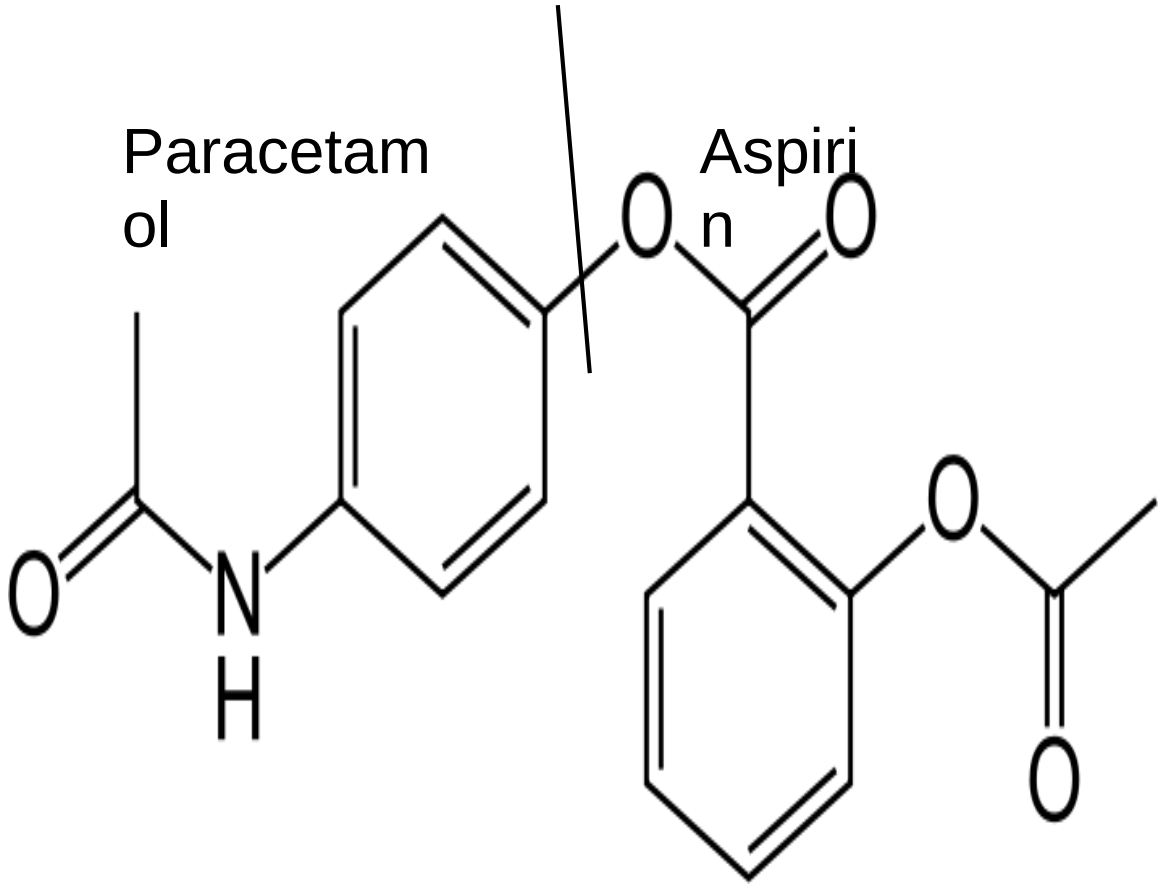
The carrier group is attached via linker/spacer to drug.



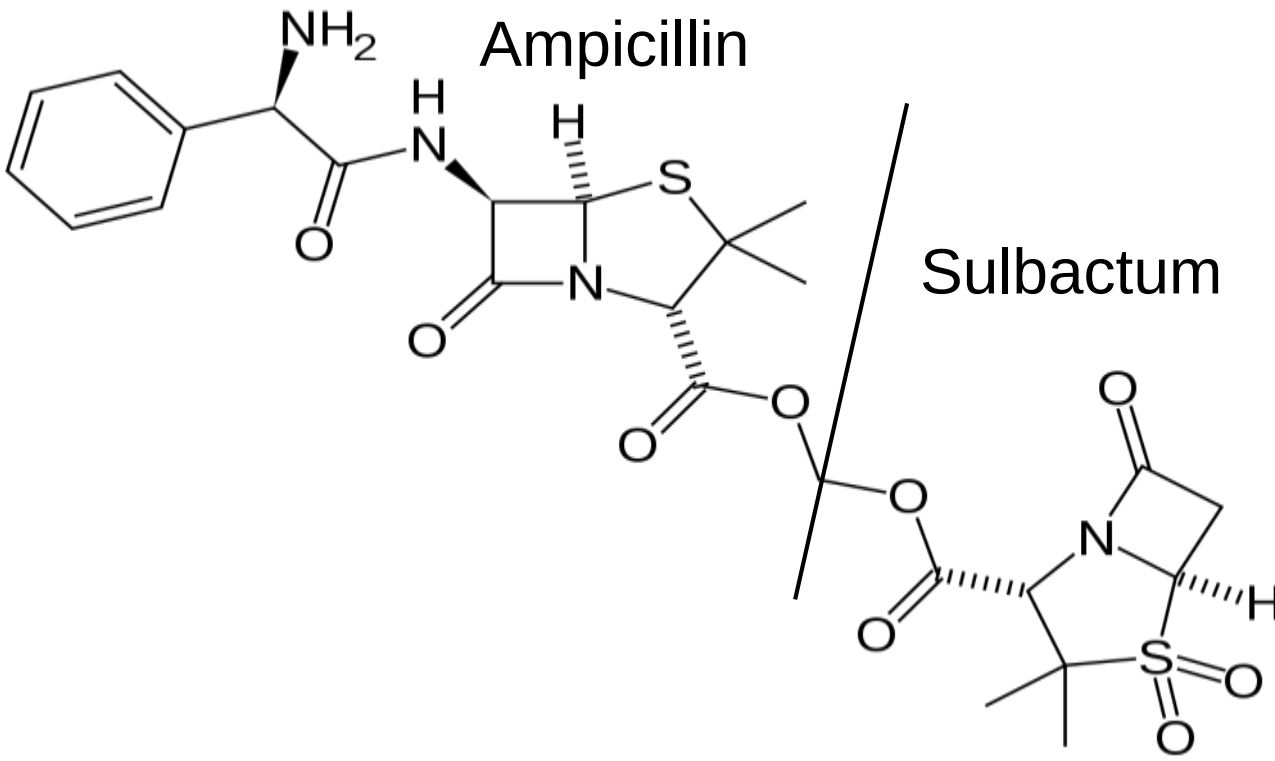
Mutual Prodrugs

- A mutual prodrug consists of two pharmacologically active agents coupled together so that each acts as a promoiety for the other agent and vice versa.
- A mutual prodrug is a bipartite or tripartite prodrug in which the carrier is a synergistic drug with the drug to which it is linked.
- Benorylate is a mutual prodrug aspirin and paracetamol.
- Sultamicillin, which on hydrolysis by an esterase produces ampicillin & sulbactum.





**Benoryla
te**



Sultamicillin

Bioprecursors

- The bioprecursor does not contain a temporary linkage between the active drug and carrier moiety, but designed from a molecular modification of an active principle itself.
- Eg: phenylbutazone. Phenylbutazone gets metabolized to oxyphenbutazone that is responsible for the anti inflammatory activity of the parent drug

• Polymeric Prodrugs

- Also known as macromolecular prodrug, the drug is dispersed or incorporated into the polymer (both naturally occurring and synthetically prepared) system without formation of covalent bond between drug and polymer.
- Eg: p–phenylene diamine mustard is covalently attached to polyamino polymer backbone polyglutamic acid.

Novel Classification

- Type I Prodrugs
- Type II Prodrugs

- Type I prodrugs are bioactivated inside the cells (intracellularly). Examples of these are anti-viral nucleoside analogs that must be phosphorylated and the lipid-lowering statins.

- Type II prodrugs are bioactivated outside cells (extracellularly), especially in digestive fluids or in the body's circulation system,

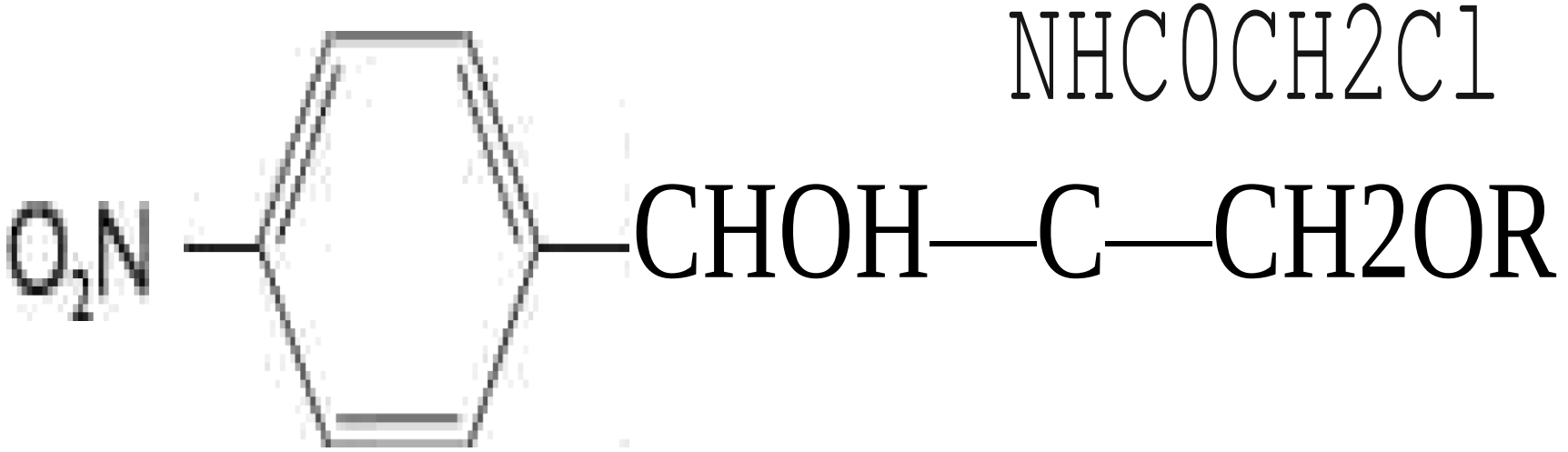
Type	Bioactivation site	Subtype	Tissue location of bioactivation	Examples
Type I	Intracellular	Type IA	Therapeutic target tissues/cells	Acyclovir,fluorouracil, cyclophosphamide,diethylstilbestrol diphosphate,L-DOPA, mercaptopurine, mitomycin, zidovudine
		Type IB	Metabolic tissues (liver, GI mucosal cell, lung etc.)	Carbamazepine, captopril, carisoprodol, heroin, molsidomine, leflunomide, palipe ridone,phenacetin, primidone, psilocybin, sulindac, fursultiamine, codeine
Type II	Extracellular	Type IIA	GI fluids	Loperamide oxide, oxyphenisatin, sulfasalazin
		Type IIB	Systemic circulation and other extracellular fluid compartments	Acetylsalicylate, bacampicillin, bambuter ol, chloramphenicol succinate, dipivefrin, fosphenytoin,lisdex amfetamine, pralidoxime
		Type IIC	Therapeutic target tissues/cells	ADEPTs, GDEPs, VDEPs

Applications of Prodrugs

Pharmaceutical applications

❑ Masking Taste or Odour

- Undesirable taste arises due to adequate solubility and interaction of drug with taste receptors.
- It can be solved by lowering the solubility of drug or prodrug in saliva.
- Eg: chloramphenicol palmitate is the sparingly soluble of prodrug of chloramphenicol, which is practically tasteless due to its low aqueous solubility, as well as it is hydrolysed to active chloramphenicol by the action of pancreatic lipase.
- Eg:Ethyl mercaptan has a boiling point of 25ºC and a strong disagreeable odour. But diethyl dithio isophthalate, prodrug of ethyl mercaptan has a higher boiling point and is relatively odourless.

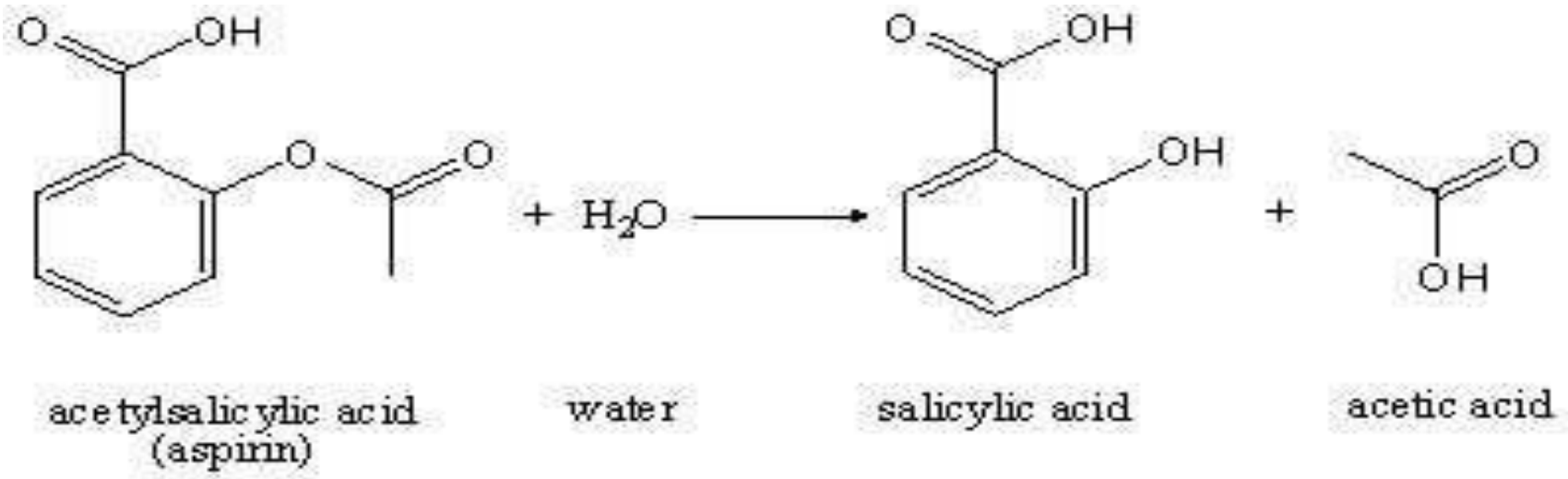


Chloramphenicol, R=H

Chloramphenicol palmitate, R= $CO(CH_2)_{14}CH_3$

❑ Reduction of gastric irritation

Eg: Aspirin is a prodrug of salicylic acid is designed to reduce gastric irritation

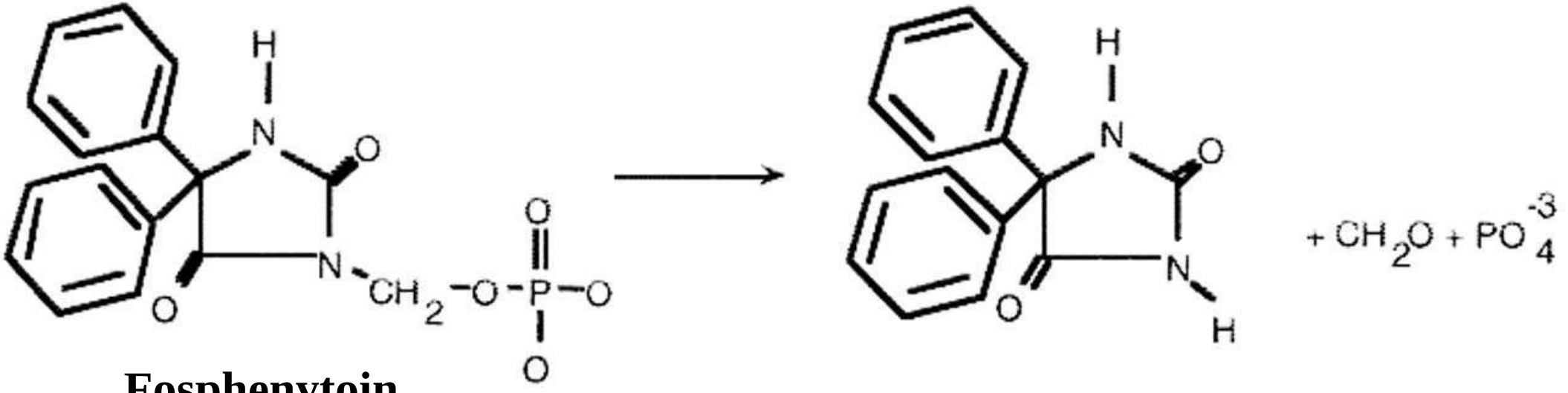


Drug	Prodrug
Salicylic acid	Aspirin
Diethyl stilbestrol	Fosfestrol
Kanamycin	Kanamycin pamoate
Phenylbutazone	N-methyl piperazine salt
Nicotinic acid	Nicotinic acid hydrazide

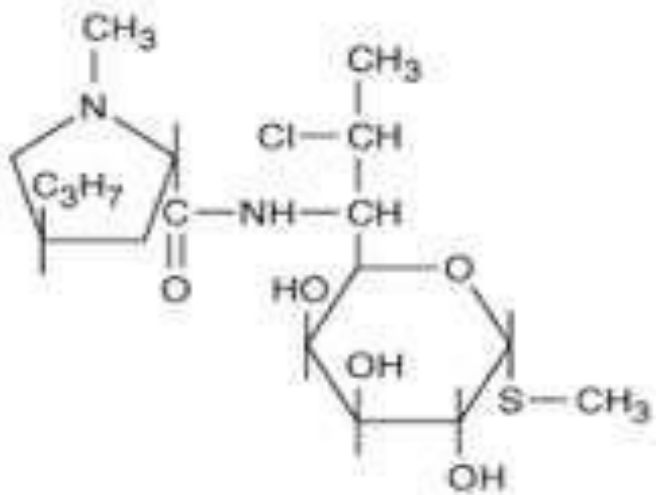
Oleandrin	oleandrin acetate

❑ Reduction in Pain at Site of Injection

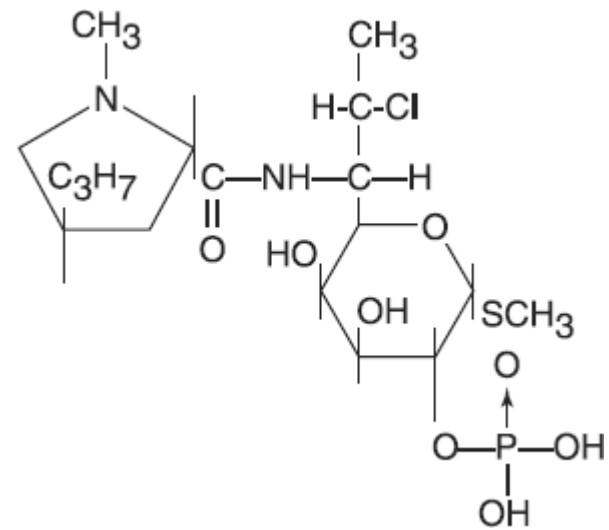
- Pain caused by intramuscular injection is mainly due to the weakly acidic nature or poor aqueous solubility of drugs.
- Eg: IM injection of antibiotics like clindamycin and anti convulsant like phenytoin was found to be painful due to poor solubility. So, prodrugs are produced like
  2'phosphate ester of clindamycin and hydantoic ester prodrug of phenytoin (fosphenytoin) an aqueous soluble form of phenytoin respectively.



Fosphenytoin **Phenytoin**



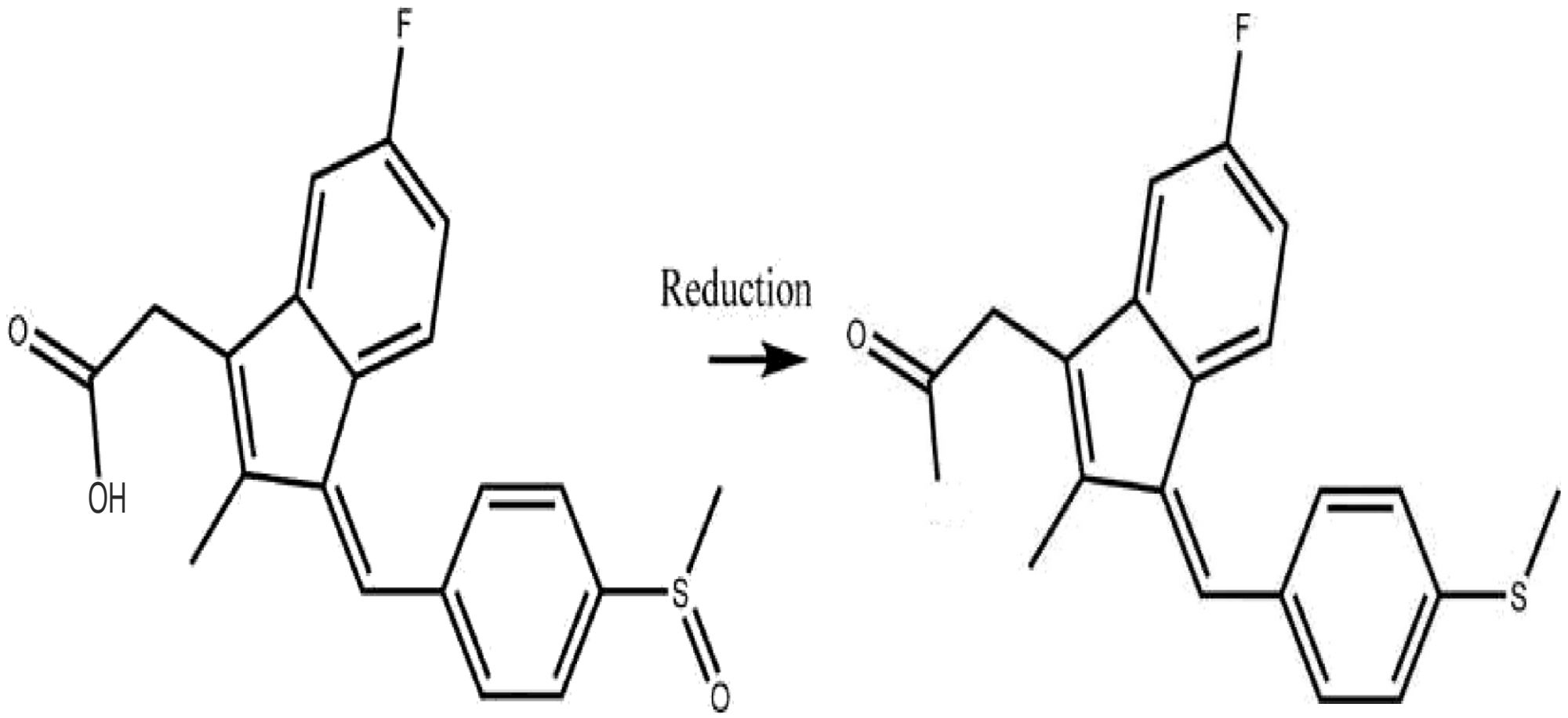
Clindamycin



Clindamycin–2 dihydrogen phosphate

❑ Enhancement of drug solubility and dissolution rate

- The prodrug approach can be used to increase or decrease the solubility of a drug, depending on its ultimate use.
- Eg: chloramphenicol succinate and chloramphenicol palmitate, ester prodrugs of chloramphenicol, have enhanced and reduced aqueous solubility respectively. On the basis of altered solubility, chloramphenicol sodium succinate prodrug is found suitable for parenteral administration.
- The prodrug approach is also made useful for better gastrointestinal absorption.
- Eg: sulindac, a prodrug of sulindac sulfide being more water soluble with sufficient lipophilicity, makes this drug suitable for oral administration
- Testosterone - testosterone phosphate ester
- Tetracycline - tetralysine
- Diazepam - diazepam L-lysine ester



R,S•sulindzc prodrug

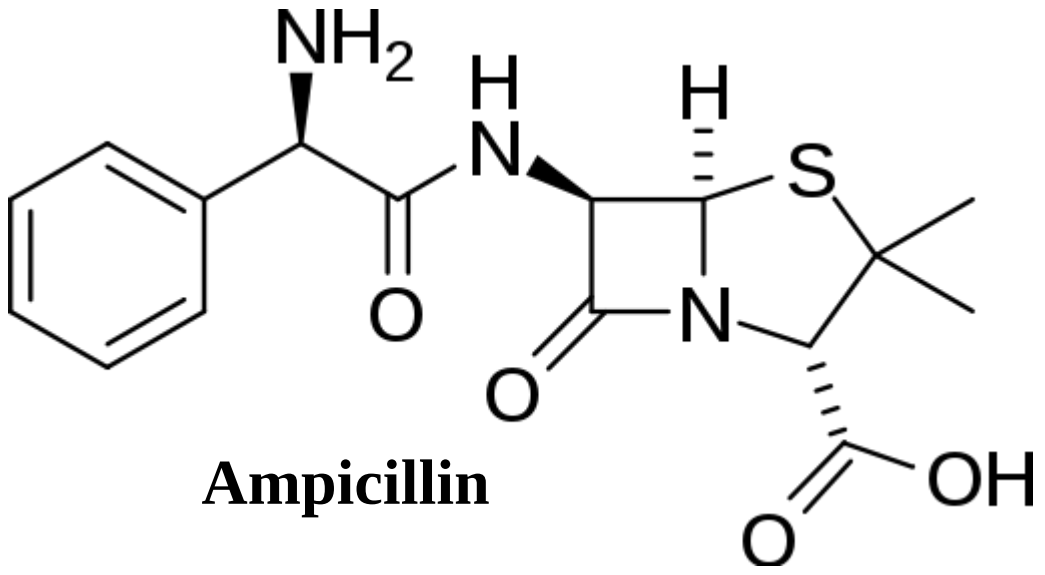
Svlindac sulfide,»ctive NSAID

❑ Enhancement of chemical stability

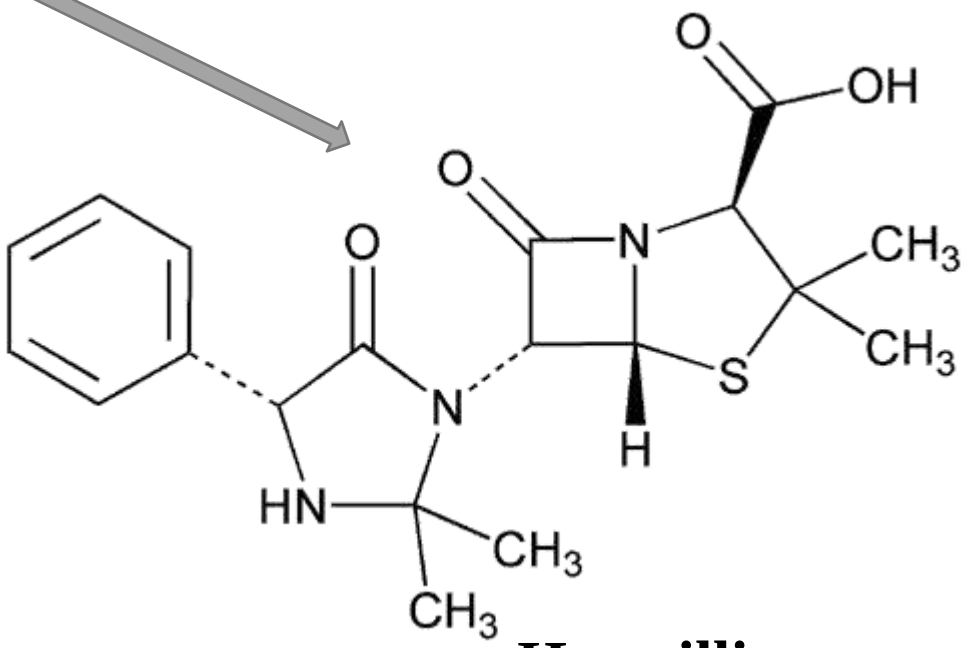
- Chemical stability is an utmost necessary parameter for every therapeutic agent.

- The prodrug approach is based on the modification of the functional group responsible for the instability or by changing the physical properties of the drug resulting in the reduction of contact between the drug and the media in which it is unstable.

- Eg: Inhibiting the auto aminolysis, which occur due to capability of NH_2 group of side chain to attach β lactam ring of other molecule, in ampicillin molecule in concentrated solution it generates polymeric species of ampicillin. By making hetacillin, a prodrug of ampicillin formed by the reaction of acetone and ampicillin „ties up“ the amine group and thus inhibits auto aminolysis



Ampicillin



Hetacillin

Pharmacokinetic Applications

❑ Improvement of Bioavailablity

➢ Enhancement of Oral Bioavailablity

- Various therapeutic agents such as water soluble vitamins, structural analogues of natural purine and pyrimidine nucleoside, dopamine, antibiotics like ampicillin and carbenicillin, phenytoin and cardiac glycoside such as gitoxin suffers with poor gastrointestinal absorption.

- The prime cause of the poor absorption of these agents is their highly polar nature, poor lipophilicity and/or metabolism during the absorption process.

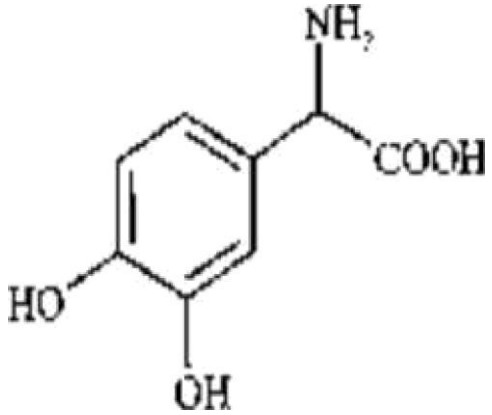
- On contrary gitoxin, a cardiac glycoside has very poor oral bioavailability due to limited aqueous solubility

- Absorption of water soluble vitamin was enhanced by derivatization of thiolate ion to form lipid soluble prodrugs .

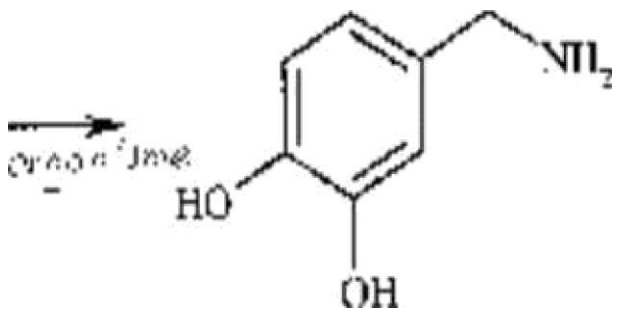
- Dopamine was made useful by making its precursor L-Dopa. Though L-Dopa is highly polar, it is actively transported through specific L–amino acid active transport mechanism and regenerates dopamine by decarboxylation.

- Penta acetyl prodrug of gitoxin has four to five times more aqueous solubility.

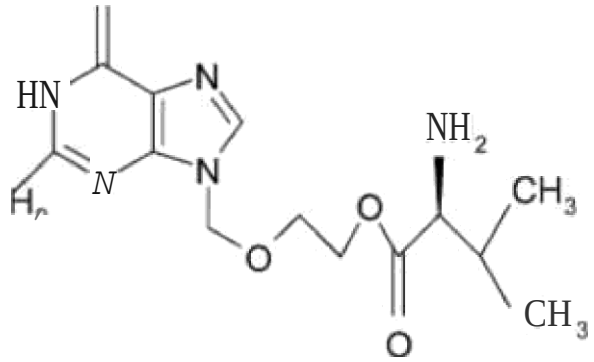
- To increase aqueous solubility esterification with amino acids is done. Examples of such prodrugs are valacyclovir and valgancyclovir, which are valine esters of the antiviral drugs acyclovir and gancyclovir, respectively.



L-Dopa

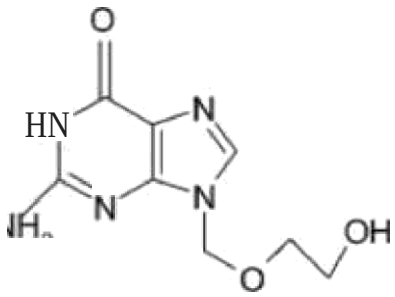


Dopamine

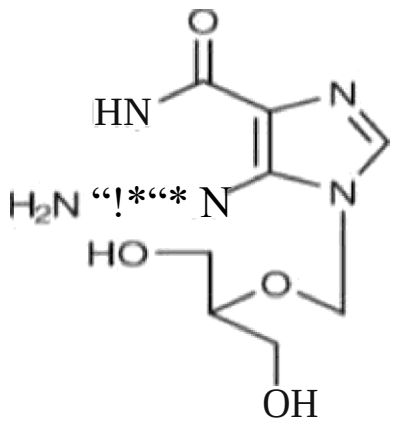


HCL

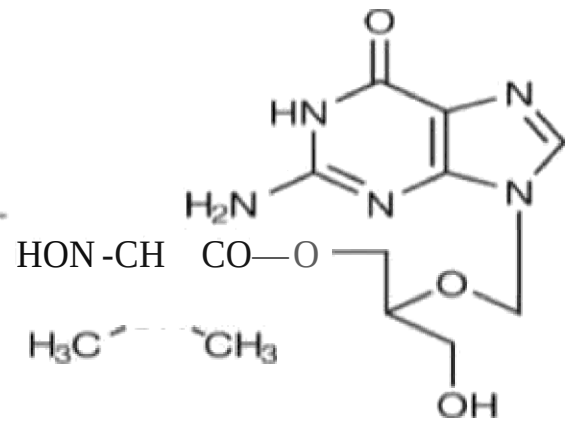
Valacyclovir HC



Acvclovir



Ganciclovlr



Valga nc iclovi r

- **Enhancement of ophthalmic bioavailability**
  - Epinephrine - dipivalyl derivative
  - Latanoprost and travoprost - isopropyl esters of latanoprost acid and travoprost acid

- **Enhancement of percutaneous bioavailability**
  - Mefenide - mefenide hydrochloride/acetate

- **Enhancement of topical administration**
  - Ketolac - Esters of ketolac

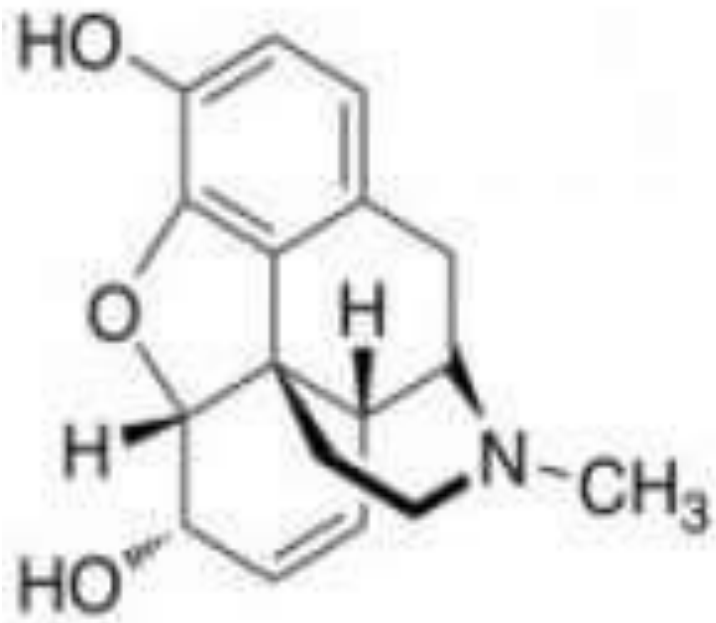
❑ Prevention of Presystemic metabolism

- Following oral administration, a drug must pass through two metabolizing organs i.e., liver and gastrointestinal mucosa, before reaching the general circulation.
- Phenolic moiety, oxidative N– and O– dealkylation, ester cleavage and peptide degradation are responsible for the pre-systemic metabolism of various drugs.
- Two types of drugs fall into this category.
- The first are drugs rapidly degraded by the acid condition of the stomach and the
- Drugs of second category degrade due to enzymes present in the gastrointestinal mucosa and liver.

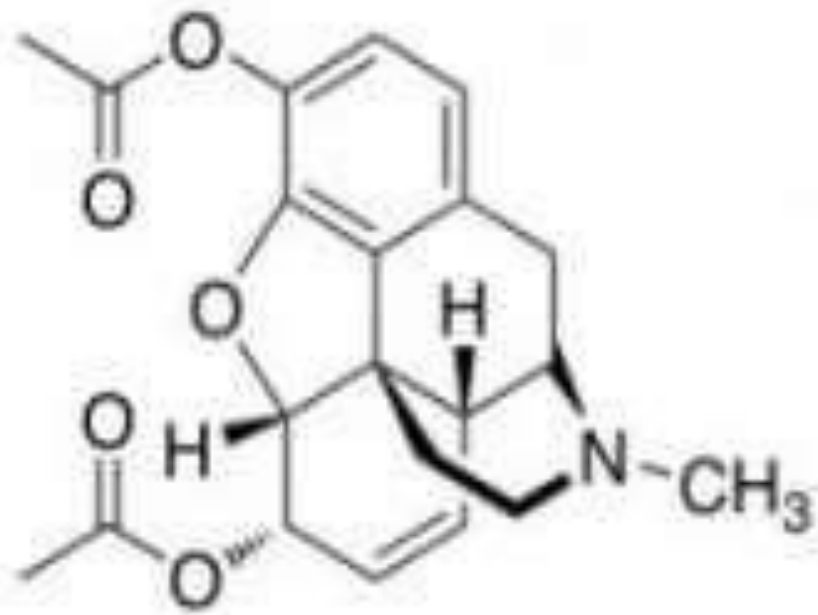
- Prodrugs may protect a drug from presystemic metabolism.

- Naltrexone (treatment of opioid addiction) and is readily absorbed from GIT and hence undergoes Presystemic metabolism. Ester prodrugs such as O-nitrobenzoate and acetylsalicylate increased bioavilablity 45 and 28 fold respectively.

Drug	Prodrug
Propranolol	Propranolol hemisuccinate
Dopamine	L-DOPA
Morphine	Heroin



morphine



heroin

❑ Prolongation of duration of action

- Drugs with short half life require frequent dosing with conventional dosage forms to maintain adequate plasma concentration of the particular drug.
- In plasma level time profile and consequently patient compliance is often poor.
- Prolongation of duration of action of a drug can be accomplished by the prodrug . Prodrug can be formed by two approaches-

❖ Control the release of the drug from complex

❖ Control the conversion of prodrug in to the parent drug.

Drug	Prodrug
Testosterone	Testosterone propionate
Estradiol	Estradiol propionate
Fluphenazine	Fluphenazine deaconate

❑ Reduction Local and Systemic Toxicity of Drugs

- An important objective of drug design is to develop a moiety with high activity and low toxicity.

- Gastric irritation and ulcerogenicity associated with aspirin use due to presence of free carboxylic group. Esterification of aspirin(R = alkyl) and other nonsteroidal anti-inflammatory agents (NSAIDs) greatly suppresses gastric ulcerogenic activity.

- Another example is the bioprecursor Sulindac, as it is a sulphoxide, it doesn't cause any gastric irritation and also better absorbed.

- The prodrug Ibuterol is iisobutyrate ester of Terbutaline (a selective β-agonist useful) in glaucoma. This prodrug, is 100 times more potent, has longer duration of action and is free from both local and systemic toxicity.

❑ Site specific drug delivery

- After its absorption into the systemic circulation, the drug is distributed to the various parts of the body including the target site as well as the non-target tissue.

- These problems can be overcome by targeting the drug specifically to its site of action by prodrug design

- The prodrug is converted into its active form only in the target organ/tissue by utilizing either specific enzymes or a pH value different from the normal pH for activation e.g. 5-amino salicylic acid.

- Tumour cells contain a higher concentration of phosphates and amidases than do normal cells. Consequently a prodrug of cytotoxic agent could be directed to tumour cells if either of these enzymes was important to prodrug activation process. Diethylstilbestrol diphosphate was designedfor site-specific delivery of diethylstilbestrol to prostatic carcinoma tissue.

❑ Site specific Drug Delivery in Chemotherapy

Directed Enzyme Prodrug Therapy (DEPT)

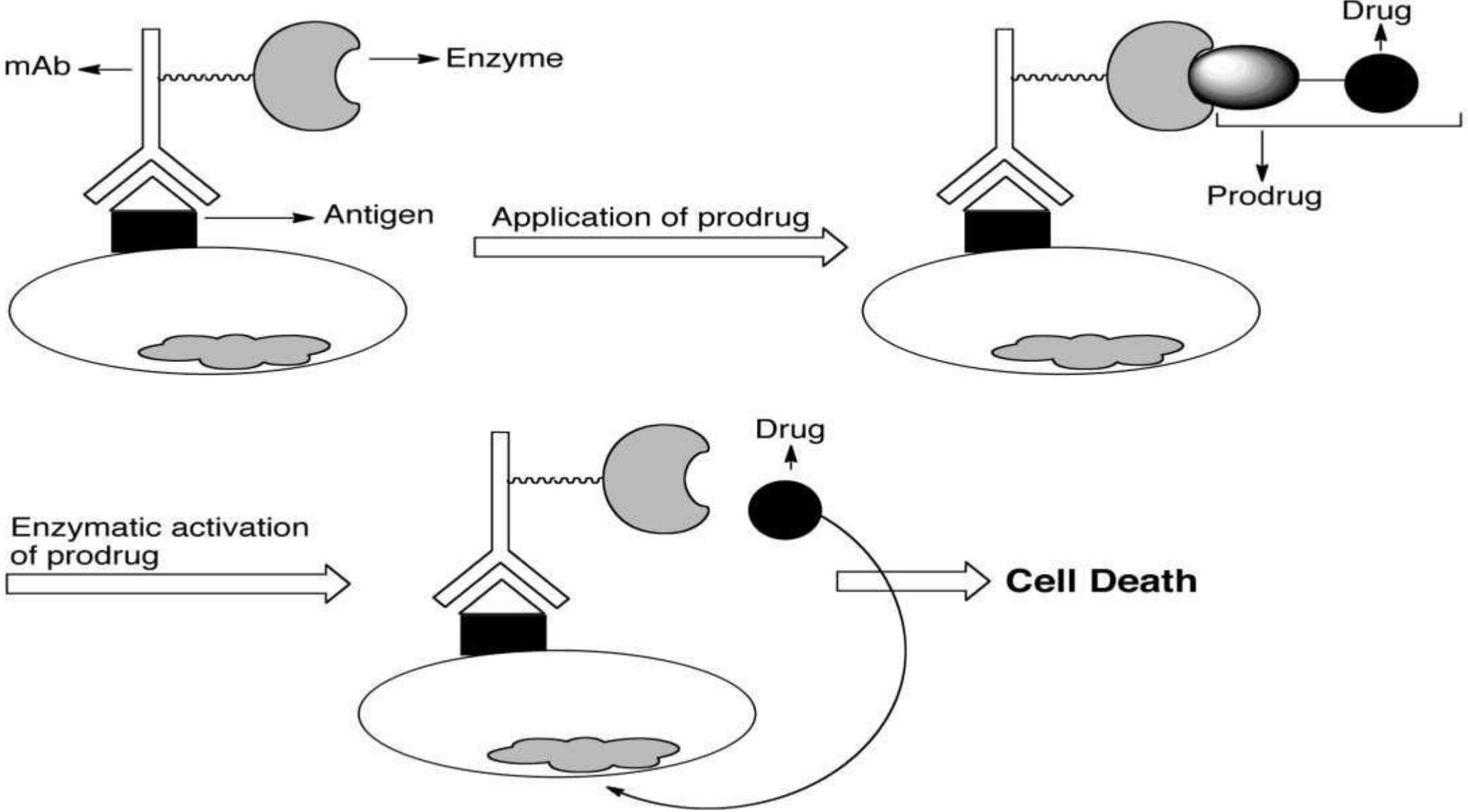
- Many chemotherapy drugs for cancer lack tumour specificity and the doses required to reach therapeutic levels in the tumour are often toxic to other tissues.
- **(DEPT)** uses enzymes artificially introduced into the body to convert Prodrugs, which have no or poor biological activity, to the active form in the desired location within the body.

- DEPT strategies are an experimental method of reducing the systemic toxicity of a drug, by achieving high levels of the active drug only at the desired site.

- Antibody-directed enzyme prodrug therapy (ADEPT)
- Gene-directed enzyme prodrug therapy (GDEPT)
- Virus-directed enzyme prodrug therapy (VDEPT)
- Polymer-directed enzyme prodrug therapy (PDEPT)
- Clostridia-directed enzyme prodrug therapy (CDEPT)

❖ Antibody-directed enzyme prodrug therapy (ADEPT)

- **ADEPT** is a strategy to overcome the problems of lack of tumour selectivity.
- An antibody designed/developed against a tumor antigen is linked to an enzyme and injected to the blood, resulting in selective binding of the enzyme in the tumor.
- A prodrug is administrated into the blood circulation, which is converted to an active cytotoxic drug by the enzyme, only within the tumor.
- Selectivity is achieved by the tumor specificity of the antibody and by delaying prodrug administration until there is a large differential between tumor and normal tissue enzyme levels.



Schematic presentation of antibody-directed enzyme prodrug therapy (ADEPT). mAb-enzyme conjugate is given first, which binds to antigens expressed on tumor surfaces. Prodrug is given next, which is converted to active drug by the pre-targeted enzyme.

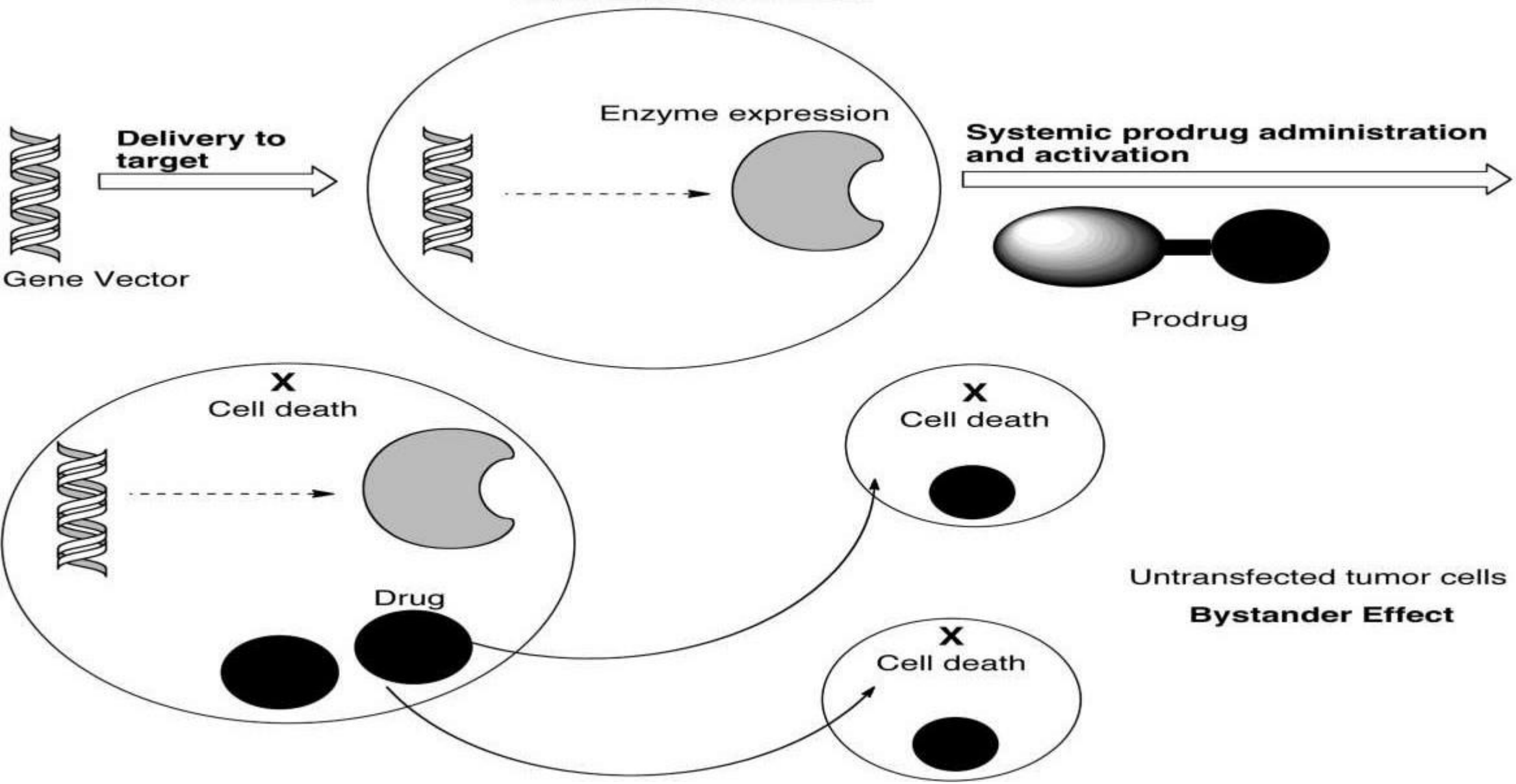
Antibody	Prodrug	Drug	Tumor target
L6	Mitomycin C phosphate	Mitomycin C	Lung adenocarcinoma
BW413	Etoposide phosphate	Etoposide	Colon carcinoma
L6	Doxorubicin phosphate	Doxorubicin	Lung adenocarcinoma

❖ Gene-directed enzyme prodrug therapy - GDEPT

- GDEPT, is a two-step process.
- In the first step, the gene for a foreign enzyme is delivered to tumor cells.
- In the second step, a non-toxic agent is administered systematically and converted by the enzyme to its cytotoxic metabolite.

Enzyme	Prodrug	Drug
Cytochrome p450	Cyclophosphamide, ifosfamide	Phosphamide mustard, acrolein
Cytosine deaminase	5-Fluorocytosine 5-Fluorouridine	5-Fluorouracyl

Nitroreductase	5-(Aziridin-1-yl)-2,4-dinitrobenzamide	5-(Aziridin-1-yl)-4-hydroxylamino-2-nitrobenzamide



Schematic presentation of gene-directed enzyme prodrug therapy (GDEPT).
Gene for foreign enzyme is transfected to tumor cells, which express the enzyme to activate the systemically administered prodrug

❖ Virus-directed enzyme prodrug therapy (VDEPT)

VDEPT is the term given to the use of a virus to deliver the gene for GDEPT. VDEPT can potentially be used to enhance the therapeutic potential of oncolytic viruses.

❖ Polymer-directed enzyme prodrug therapy (PDEPT)

PDEPT uses polymer-drug conjugates, drugs contained within a polymer 'shell' such as pHPMA and designed to be released only by a specific enzyme.

❖ Clostridia-directed enzyme prodrug therapy (CDEPT)

- **CDEPT** is the use of Clostridia to convert prodrugs into active drug agents. CDEPT exploits the hypoxic environment of solid tumors to target drugs to tumors using anaerobic bacteria resident in the tumour to convert the pro-drug to the active form.

- Solid tumours, in contrast to normal tissues, grow rapidly. As a result, the cancerous tissues may suffer from inadequate blood and oxygen supply. Therefore, clostridia can grow in tumor and destroy it specifically.

- In CDEPT, a prodrug-converting enzyme expressed by a clostridial expression plasmid converts a prodrug into an active drug form within the tumor.

- While the prodrug is the inactive form and can be administrated to the blood, the products of the prodrug cleavage are highly cytotoxic and show their effect only in the vicinity of tumor cells.

CONCLUSION

Prodrug design is a part of the general drug discovery process, in which a unique combination of therapeutically active substances is observed to have desirable pharmacological effects.

In human therapy prodrug designing has given successful results in overcoming undesirable properties like absorption, nonspecificity, and poor bioavailability and GI toxicity.

Thus, prodrug approach offers a wide range of options in drug design and delivery for improving the clinical and therapeutic effectiveness of drug.