Chapter 8: Prodrugs Concepts & Application

Prodrugs: Basic concepts and application of prodrugs design.

8.1. PRODRUG BASIC CONCEPTS

Prodrugs:

- Prodrug is a biological inactive drug which activate and produce its pharmacological effects after metabolic or physico-chemical transformation.
- Prodrugs can be found in nature, such as several phytochemicals/botanical constituents and endogenous compounds, or they can be created by synthetic or semisynthetic methods, either deliberately or accidentally throughout drug creation.
- In Pharmaceutical approach, a prodrug is a chemically modified inert drug precursor, which upon biotransformation liberates the pharmacologically active parent compound.

Historical Development

- 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 1**897 by Felix Hoffman (Bayer, Germany)**, and introduced into medicine by **Dreser in 1899**. Aspirin further converts into active compound salicylates.
- 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 **chloramphenicol palmitate** used in the form of suspension in children.

Basic Objectives and Goal of Prodrug Design

A) Formulation and pharmacological aspect's

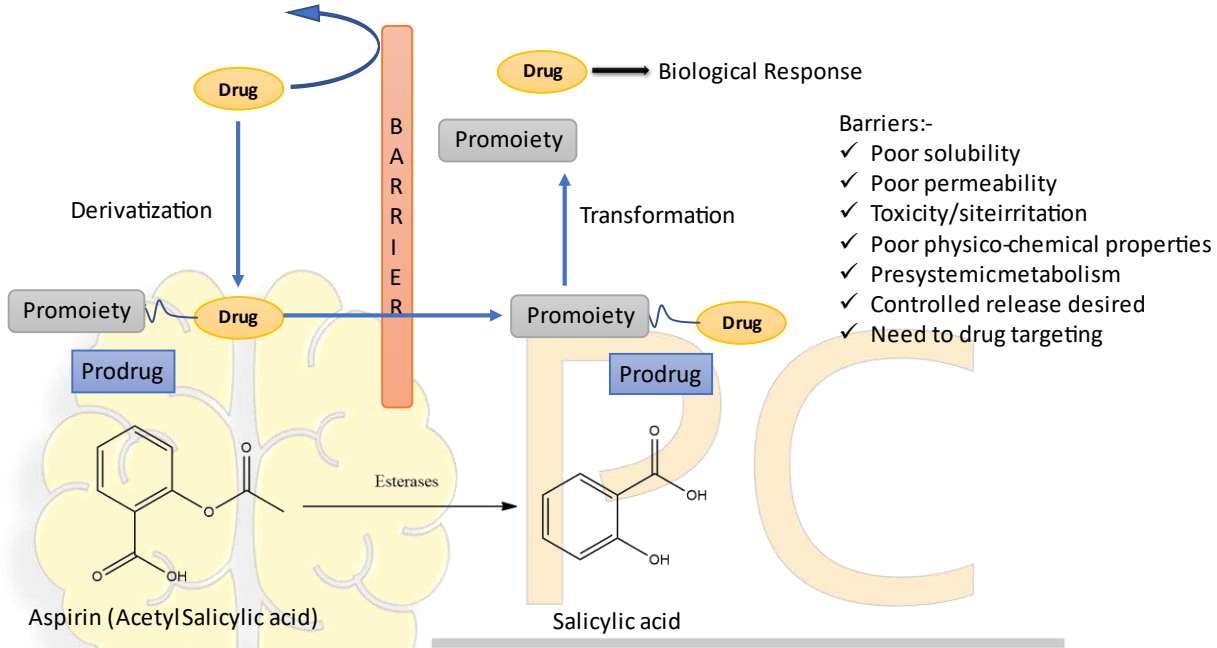
Pharmaceutical goal involves overcoming the following:

- ✓ unpleasant taste
- ✓ pain on injection
- ✓ poor solubility

- ✓ slow dissolution

Pharmacokinetic and Pharmacodynamic goal involves overcoming following:

- ✓ Poor bioavailability
- ✓ Short duration
- ✓ High first pass metabolism
- ✓ Toxicity or side effects
- ✓ Non specificity tissues and organ selectivity



B) Conversion site

After the specific challenge has been solved, the main purpose of all Prodrugs is to be quantitatively transformed to drug rapidly at conversion/target site.

A) Prolonged duration and Stability

The duration of drug in plasma is determined by 2 steps:

- ✓ The rate of input of Prodrug from site of administration to blood.
- ✓ The subsequent conversion of Prodrug to drug in blood.

The stability of Prodrug is required in two different area, they are

1) At Gastrointestinal tract

The conversion of Prodrug in intestine is a useful way for bypassing the problems other than stomach instability i.e., applicable to

- ✓ Poor soluble drugs
- ✓ Drug with bad odour and taste
- ✓ Those upset stomach.

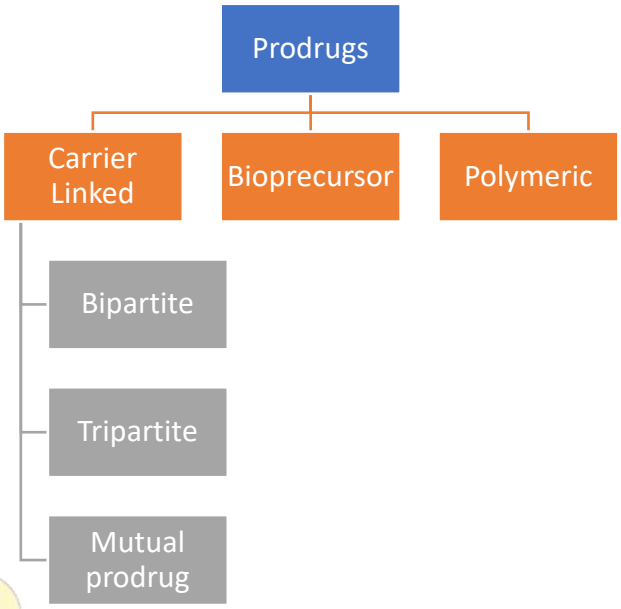
2) At storage

- ✓ The use of a prodrug extends the shelf life of a product. The medicine must be stable in storage by preventing conversion, but it must convert in vivo (inside the body).
- ✓ This requires a special mechanism known as Trigger. A trigger may be based on availability of enzymes in the body or on the hydrogen ion concentration difference between product and body fluid.

Table: Examples of prodrug and the purpose of modification.

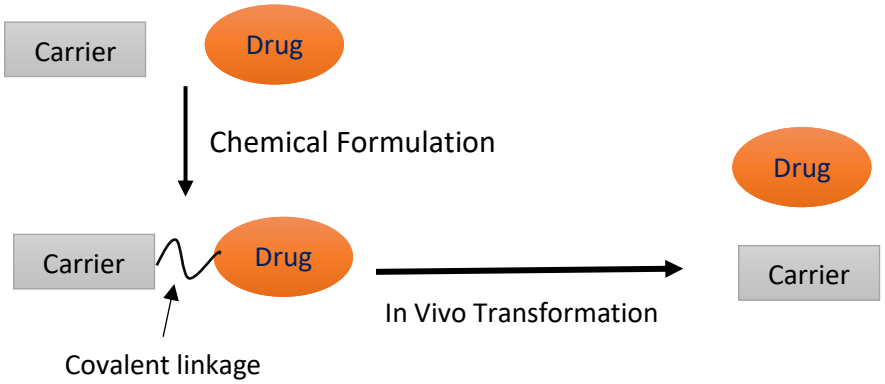
Parent Drug	Prodrug	Reason of Modification
Amoxicillin	Sarmoxicillin	Increase distribution
Ampicillin	Bacampicillin, Pivampicillin, Talampicillin	Increase distribution
Ampicillin	Hetacillin	Enhance Bioavailability; Increase stability
Chloramphenicol	Chloramphenicol palmitate ester	Improve Taste
Chloramphenicol	Chloramphenicol succinate ester	Water solubility
Clindamycin	Clindamycin palmitate ester	Improve taste
Dopamine	L-dopa	Delivery to brain
Epinephrine	Dipirefrin	Corneal penetration
Erythromycin	Erythromycin ethylsuccinate	Gastric stability
Estradiol	Estradiol cypionate	Extend duration
Fluphenazine	Fluphenazine decanoate	Long-acting depot injections
Formaldehyde	Methenamine	Urinary tract delivery
Metronidazole	Amino acid esters,	Water solubility
Testosterone	Testosterone propionate	Extend duration
Salicylic acid	Salsalate or Acetylsalicylic acid	Gastrointestinal tolerance and bioavailability
Nitrogen Mustard	Amide derivative	Delivery to neoplastic tissue

8.2. CLASSIFICATION OF PRODRUG



8.2.1. Carrier Linked Prodrug

- An inactive transporter or carrier is covalently coupled with the active drug in a carrier associated prodrug.
- They are connected by an **ester or an amide**.
- They are chemically or enzymatically bio-transformed and activate the active ingredient.
- The prodrugs added to the carriers should be non-toxic.
- They should be able to hide the negative side effects.
- They change the active drug's physiochemical properties



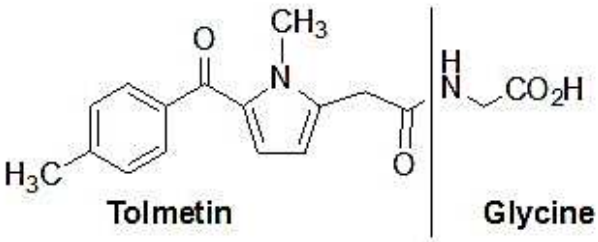
Ideal requirements of a carrier:

- ✓ It should be biologically inactive non-toxic and non-immunogenic.
- ✓ Reduce the activity of drug.
- ✓ Must minimize the toxicity of host drug.
- ✓ Should carry and release the drug at specific required site of action.
- ✓ Should allow release of drug chemically or enzymatically

Bipartite Prodrug

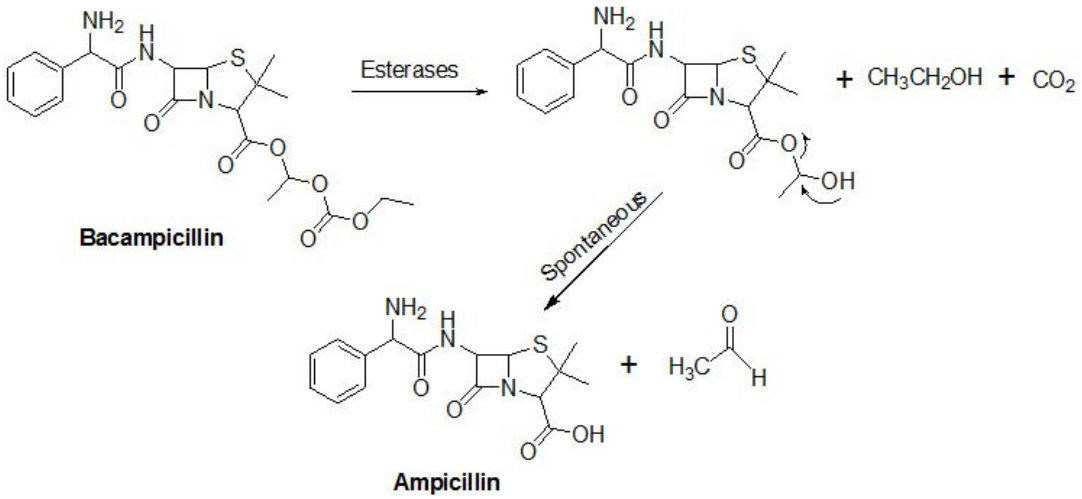
- It consists of one carrier (group) attached to the drugs.
- These prodrugs formation enhance the lipophilicity due to the attached carrier.
- The active drug is released by hydrolytic cleavage either chemically or enzymatically.

E.g. Tolmetin-glycine prodrug.



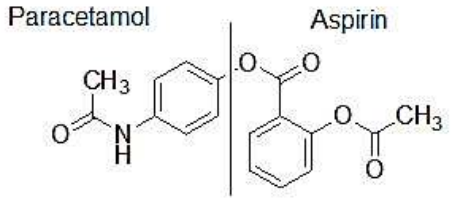
Tripartite Prodrug

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

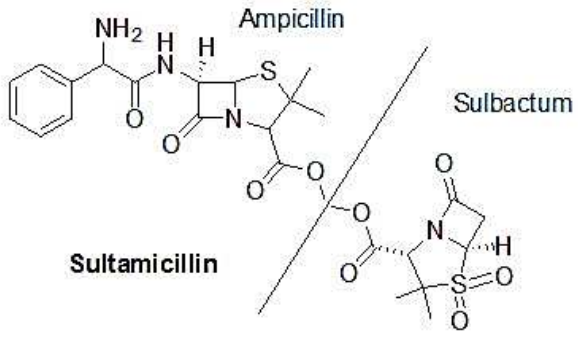


Mutual Prodrug

- 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.
- E.g., Sultamicillin (ampicillin + sulbactam), Benorylate (Paracetamol + Aspirin)



Benorylate / Benorilate

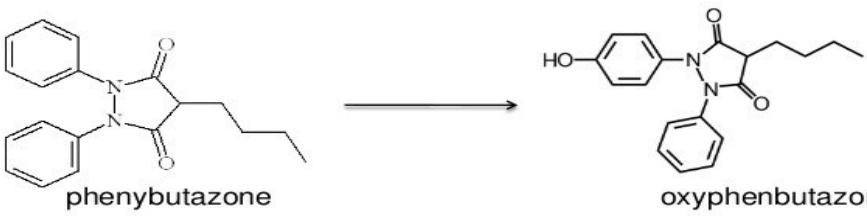


Sultamicillin

8.2.2. Bio-precursor Prodrug

- Here parent drug is obtained by redox transformation through enzymes. Here prodrug result by chemical modification of parent drug.
- The lipophilicity does not alter generally.
- 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



phenybutazone oxyphenbutazone

phenylbutazone. Phenylbutazone gets metabolized to oxyphenbutazone that is responsible for the anti inflammatory activity of the parent drug

8.2.3. Polymeric Prodrug

- 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.

8.3. APPLICATION OF PRODRUG

A) Alter the solubility.

- ✓ The prodrug approach can be used to increase or decrease the solubility of a drug, depending on its ultimate use
- ✓ Some drugs show poor solubility, in order to increase their solubility Prodrugs may be used. Example: methylprednisolone is converted to methyl prednisolone sodium succinate.
- ✓ Eg: chloramphenicol succinate and chloramphenicol palmitate, ester prodrugs of chloramphenicol, have enhanced and reduced aqueous solubility respectively. Based on altered solubility, chloramphenicol sodium succinate prodrug is found suitable for parenteral administration

B) Increase in bioavailability and Absorption

- ✓ The prodrug approach is also made useful for better gastrointestinal absorption
- ✓ Increase in lipophilicity causes increase in passive transport therefore by imparting lipophilic carrier to drug its bioavailability can be increased.
- ✓ Eg: sulindac, a prodrug of sulindac sulfide being more water soluble with sufficient lipophilicity, makes this drug suitable for oral administration
- ✓ Example: Acyclovir is converted to 6 deoxy acyclovir which is 5-6 times more bioavailable and 18 times more water soluble than parent compound.

C) Reduction of toxicity

- ✓ When the drug has toxicity, it can be reduced using the Prodrug formation.
- ✓ Example: Methotrexate an antitumor drug acts equally on both healthy and tumour cell but its poly (L- lysine) derivative is toxic only to tumour cells.

D) Prolonged action

- ✓ When the plasma half-life is decreased there will be high clearance from the body hence frequent dosing is essential but by Prodrug, the action may be prolonged to few month or more.
- ✓ Example: Fluphenazine when converted to decanoate derivative of fluphenazine it shows action for 1 month.

E) Target drug delivery

- ✓ Site specific drug release causes maximum drug absorption avoiding toxicity associated with availability of drug in non-target area as well as early biotransformation of drug. The second approach used to increase target drug delivery are:
- ✓ Alteration in hydrophilic or lipophilic properties of drug/coupling the drug with special site- specific carrier molecule to direct drug to target site.
- ✓ Site specific activation of Prodrug molecule to release the drug.

F) Improvement in patient compliance

- ✓ Generally, patient will not take drugs which are unpalatable in taste and odour so solubility in saliva and in turn contact with taste buds can be minimized by the esterification of drugs with long chain fatty acids
- ✓ Example: Clindamycin palmitate less bitter than clindamycin.

Overall summary of Application:

- ✓ Improve patient acceptability.
- ✓ Alter and improve absorption.
- ✓ Alter biodistribution.
- ✓ Alter metabolism.
- ✓ Alter elimination.
- ✓ Drugs is not (sufficiently) bioavailable.
- ✓ Drug does not permeate the blood-brain barrier (dopamine, GABA).
- ✓ Drug has poor properties (solubility, taste).
- ✓ Drug has no (sufficient) chemical stability (active principles of acetylsalicylic acid, isoniazid, omeprazole, clopidogrel).

- ✓ Drug has no (sufficient) organ or cell specificity (sulfamethoxazole, capecitabine, acyclovir)
- ✓ 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.