

PRODRUG DEVELOPMENT

Abstract

History: Since from the late 19th century, Prodrug approach has been used to enhance undesirable drug characteristics, Adrien Albert first used the term "Prodrug" at the end of the 1950s to describe drugs that are inactive on their own but transform into an active derivative through biotransformation in 1958. In 1959, Harper finished the idea and coined the phrase called "drug latentiation" to describe medications that need bioactivation was first used [1]. Acetanilide was originally used as a Prodrug in 1867 by Cahn and Hepp, who also brought it to medicine. The biologically active molecule acetaminophen, which has both antipyretic and analgesic properties, is created in the body when acetanilide is subjected to hydroxylation.

Definition: The IUPAC defines a Prodrug as a molecule that goes through biotransformation before revealing pharmacological effects, which is still the definition that applies today.

Prodrug: A pharmacologically inactive drug or substance that becomes an active drug after being consumed and undergoes metabolization in the body.

Keywords: Prodrug Development, Bioprecursors, Biotransformation, Drug Latentiation.

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I. INTRODUCTION

Prodrug that, through chemical or enzymatic cleavage, undergoes some *in-vivo* biotransformation, possessing the ability to transform into the active parent medicine inside the human body and allowing the administration of the active molecule at effective levels. Prodrugs are typically developed to boost bioavailability when a treatment is inadequately absorbed from the digestive tract. When a medicine interacts with cells that are not its intended target, a Prodrug can help the drug engage with them more selectively^[2,3,4]. The Prodrug technique is used to optimize recently discovered chemical entities as well as to enhance the qualities of medications that have already been put on the market. Utilizing the prodrug approach, is a technique used to enhance the pharmacokinetics profile of a drug to overcome physical, chemical, biological, and organoleptic obstacles of few drugs that are currently on the market have low bioavailability and patient non compliance. It is one of the way to improve pharmacokinetic profile of the drug.

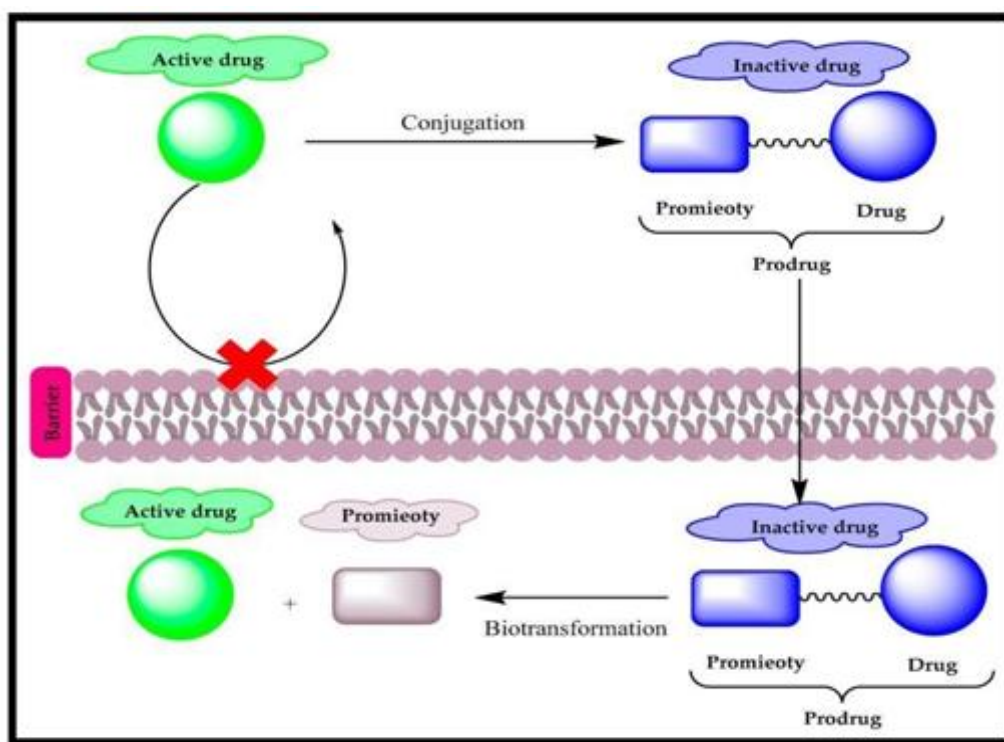


Figure 1: Diagrammatic representation of Prodrug approach^[5]

In order to achieve optimal oral bioavailability and subsequent therapeutic effect, Prodrug concept is used to overcome Biopharmaceutic (Bioavailability and Bioequivalence), Pharmacokinetic (ADME), or Pharmacodynamic (what a drug does to the body) challenges, such as inadequate chemical stability, solubility constraints, a lack of site-specificity, substantial drug metabolism, overcoming biological barriers, leveraging endogenous metabolic processes, harmful effects, or difficulties with compliance (unpleasant taste (or) odour), in the last ten years, the U.S.F.D.A has approved about 30 Prodrugs (12% of them are novel small-molecule chemical substances). Prodrugs are thought to make up about 10% of all commercially marketed medications worldwide.

The Prodrug strategy was once thought of as a last option in the development of drugs. However, today it is also taken into consideration at the very beginning phases of drug research & development. While creating (or) designing Prodrug does include utilizing a brand-new chemical entity, the expense is lower than that of creating a novel drug medicine development is accelerated by the better performance (in comparison to the parent medicine), which could ultimately result in time, money, and effort savings.

1. Benefits of Prodrugs ^[6]:

Here are several justifications for employing the Prodrug method in drug development:

- Improved solubility in water.
- Enhanced distribution and absorption.
- Site particularity.
- Increased drug stability.
- Long-term release.
- Decreasing toxicity.
- Inadequate patient acceptance.

2. The Objectives of Creating Prodrugs ^[7]: Prodrug design specifically aims to maximize chemical or metabolic stability, optimize undesirable physicochemical features, and achieve desired delivery.

Increasing bioavailability when a drug candidate lacks the attributes of a medicine because they have undesirable physical characteristics, such as:

- Poor solubility in water.
- Reduced lipophilicity.
- Unpleasant odors or tastes.
- Soreness and discomfort localized.

Enhancing bioavailability when the drug candidate is not a medicine because of its pharmacokinetics:

- Minimal bioavailability.
- The inability of biological membranes to be penetrated.
- Higher first-pass metabolism.
- Parenteral route lagging absorption.
- Quick absorption/elimination as opposed to prolonged effects.
- Lacking in specificity in some tissues.

The benefits of Prodrugs with improved pharmacokinetic characteristics include:

- Enhancing gastrointestinal absorption following oral delivery.
- The acquisition of parenteral preparations.

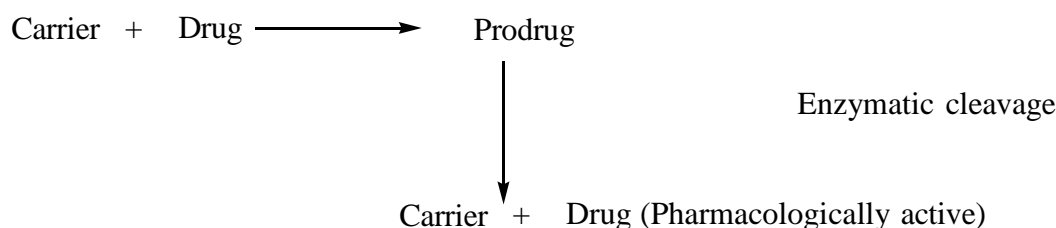
- Disguising offensive flavors and scents.
- Preventing pain or irritation at the injection site.
- Preventing quick shutdown of the administration site.
- Facilitating crossing of the blood-brain barrier.
- Medication delivery to specific tissues or organs.
- Decreasing the use of multiple drugs.
- Toxicity profile and side effects have improved.

Prodrugs have the potential to be safer, more convenient, and more effective than traditional medications.

II. PRODRUGS CLASSIFICATION [8]:

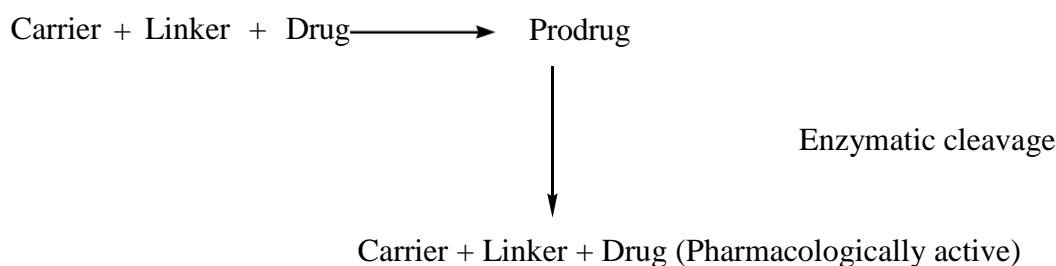
1. Based on Structural Association of Molecules: Prodrugs are divided into two major categories

- **Carrier-Linked Prodrugs:** Further classified into four types
 - **Bipartite Prodrugs:** These prodrugs have the carrier connected to the parent substance directly.



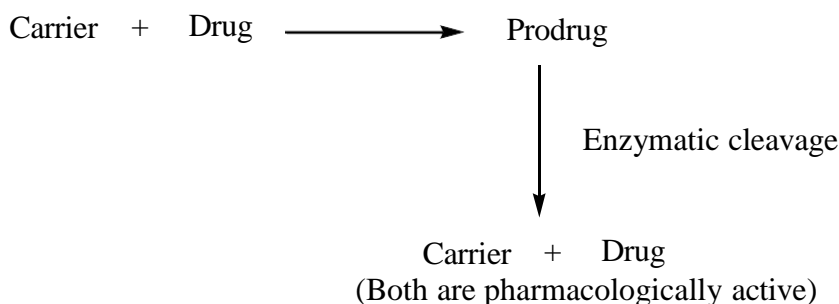
Examples: Prednisolone sodium phosphate, latanoprost, dipivefrin, etoposide phosphate.

- **Tripartite Prodrugs:** A spacer connects the carrier and parent drug in this type of **prodrug**. Carriers are typically joined together using chemical groups like amide, carbonate, ester, ether, carbamate, imine, and phosphate are frequently used to link carriers to one another.



Examples: Pivampicillin, Bicampicillin.

- **Mutual prodrugs** - In the co-drug* strategy, two Pharmacologically active chemicals are mixed and one serves as a promoter for the other in which it has two linked active molecules, Through their combined effects, these Prodrugs are more effective.



Examples: Estramustine, Sultamucilin.

- **Macromolecular Prodrugs:** It is a different kind of carrier-linked prodrug that utilizes polymeric backbones as a carrier. To create prodrugs that will cleave inside a cell and in targeted drug-delivery devices, Improved medication solubility, stability, release, and pharmacokinetics are all benefits of this strategy. Examples: Ribavarin.
- **Bioprecursors:** Bioprecursors are inactive substances without a carrier that are quickly transformed into active drugs through metabolic reactions, which are typically redox reactions.

One of the most important aspects to consider when creating Prodrugs is the activation mechanism, which releases the active parent drug from the Prodrug in an effective and well-characterized manner to achieve the therapeutic purpose, as was before discussed. Prodrug activation can occur either chemically (for instance, through oxido-reduction) or through hydrolysis caused by an enzyme. These enzymes include transferases, lyases, hydrolytic enzymes (such as carboxylesterases, phosphatases, and esterase), oxidoreductases (such as cytochrome P450), and hydrolytic enzymes.

Examples: Prontosil, Sulindac.

2. Based on how the Prodrug is Transformed by the Body in to the Actual Active Medication For: Prodrugs can be divided into two major categories.^[9]

- **Type-I:** Intracellular bioactivation which most usually takes place in the Statins, which decrease cholesterol, and antiviral nucleoside analogs that need phosphorylation.
- **Type-II:** Extracellular bioactivation, which most usually takes place in the blood or the body's circulatory system, more frequently. Example: chemotherapeutic or immunotherapy prodrugs.

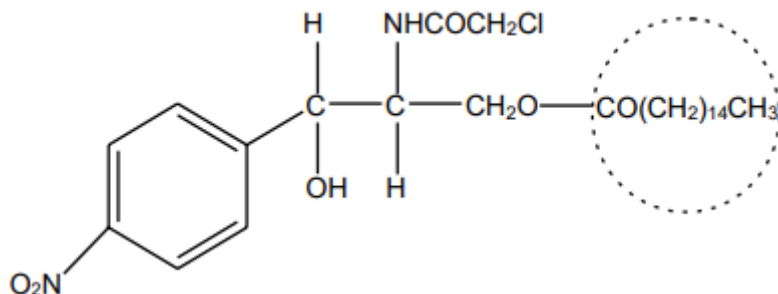
Classification of ProDrugs				
Class	Site of Bio Activation	Associated Type	Tissue of Bio location	Few Examples
Class I	Intracellularly Bio Active	Sub Type (or) Sub Class IA	Therapeutic target cells(or) tissues	Aciclovir, Fluorouracil, zidovudine, Cyclophosphamidediethylstilbestroidiphosphate, Mitomycin, L- DOPA, Mercaptopurine.
		Sub Type (or) Sub Class IB	Metabolic tissues including the liver, GI mucosal cells, and the lungs	Carbamazepine, Phenacetin, Heroin, Molsidomine, Leflunomide, Paliperidone, Primidone, Psilocybin, Sulindac, and Fursultiamine, Captopril, Carisoprodol.
class II	Extracellularly Bio Active	Sub Type (or) Sub Class IIA	Gastro Intestinal fluids	Oxyphenisatin, Sulfasalazine, Loperamideoxide.
		Sub Type (or) Sub Class IIB	extracellular fluid compartments, the systemic circulation, and other regions	Acetylsalicylic acid, Bactrim, Bacampicillin, Bambuterol, Chloramphenicol succinate, Dipivefrin, Fosphenytoin, Lisdexamphetamine, Pralidoxime.
		Sub Type (or) Sub Class IIC	tissues or cells used for therapy	Antibody-directed Enzyme Prodrug Therapy's, Gene- directed Enzyme Prodrug Therapy's, Virus - directed Enzyme Prodrug Therapy's, Lectin - directed Enzyme Prodrug Therapy's, polymer - directed Enzyme Prodrug Therapy's, Clostridia - directed Enzyme Prodrug Therapy's.

III. THERAPEUTIC APPLICATIONS OF PRODRUGS ^[10,11,12,13].

1. Undesirable Taste of Many Drugs can be altered by Converting into Prodrug

- Undesirable taste is due to its solubility and interaction with taste receptors so it can be reduced by decreasing the polarity of the drug by attaching non polar functional groups.
- Chloramphenicol is an antibiotic which is very bitter in taste due to its aqueous solubility. The bitter taste of this drug is reduced by converting into Chloramphenicol palmitate which is a sparingly soluble prodrug of Chloramphenicol. After

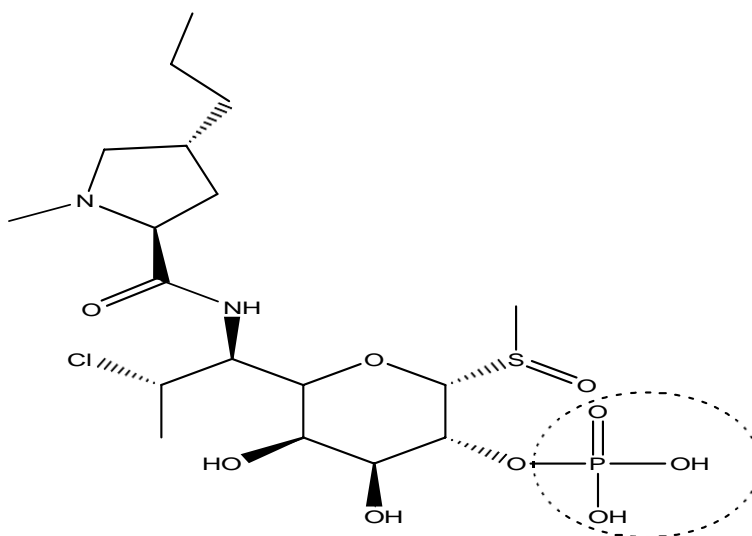
administration by the action of pancreatic lipase which hydrolyses and releases Chloramphenicol and exerts its pharmacological action.



Chloramphenicol Palmitate

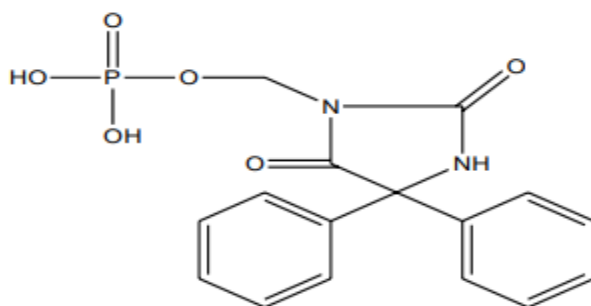
2. Reduces Pain at the Site of Injection

- Some drugs upon IM administration produces pain at the site of injection this due to its weak acidic nature or less solubility which gets deposited in the tissues and causes necrosis results in pain so it can be reduced by enhancing the solubility by attaching polar function groups.



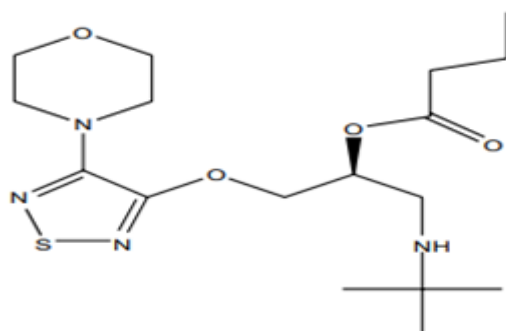
Clindamycin-2-phosphate

- Clindamycin is an antibacterial agent used orally in the treatment of gram-positive and anaerobic infections. When it administered IM produces pain at site of injection, which is overcome by converting into prodrug clindamycin 2-phosphate. After injection it is rapidly converted into clindamycin in presence of phosphatase. Clindamycin 2-phosphate, unlike clindamycin, is highly water soluble and does not produce pain upon injection.
- Phenytoin is an anticonvulsant drug which upon IM administration produces pain at the site of injection, which can be reduced by converting it into Fosphenytoin.



Fosphenytoin

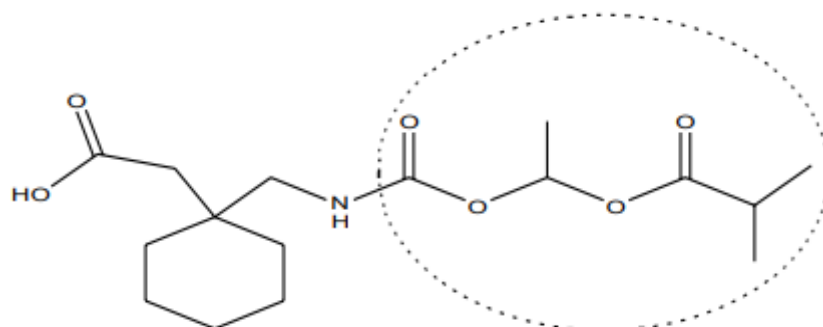
- A drug called timolol is used to treat and manage ocular hypertension and open-angle glaucoma. It is a medication from the beta-blocker group. Although timolol naturally has a very low log P value, it can become more lipophilic by being converted into butyryltimolol.



Butyryl timolol

3. Site Directed Drug Delivery

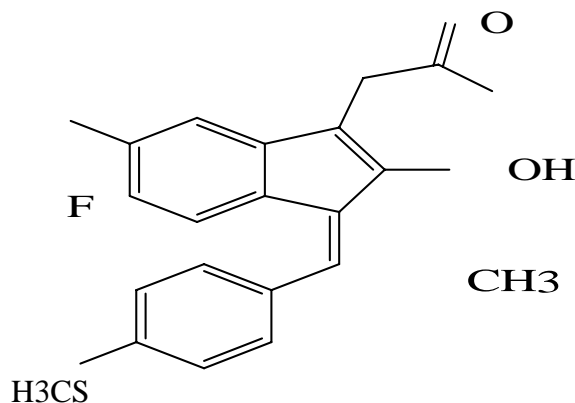
- Various drugs due to their instability they bypass various pharmacokinetic and pharmaceutical barriers after administration. Gabapentin is having less absorption, bioavailability and pharmacokinetic properties these problems overcome by prodrug Gabapentin enacarbil which is used to treat moderate-to-severe primary Restless Legs Syndrome (RLS).



Gabapentin enacarbil

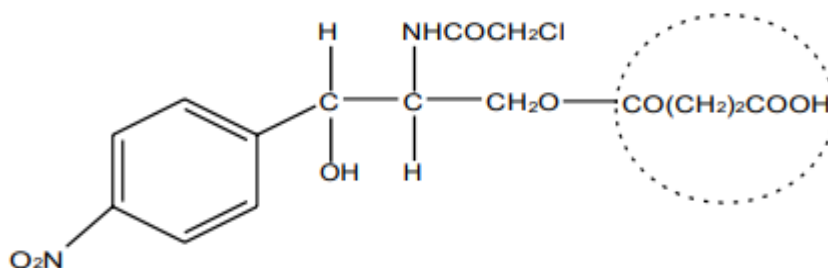
4. Improvement of Drug Solubility and Dissolution Rate

- Prodrug approach can be used to increase or decrease the drug solubility depending on its ultimate use. Sulindac sulfide is the active form of sulindac which is generally used as anti-inflammatory agent, which is being more water soluble with sufficient lipophilicity, makes this drug suitable for oral administration.



Sulindac sulfide

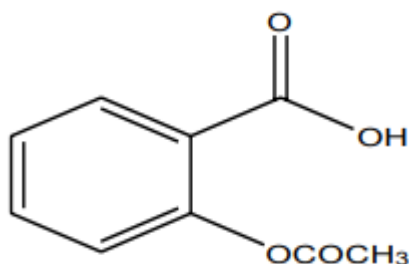
- The prodrugs of the chloramphenicol ester class chloramphenicol succinate and chloramphenicol palmitate have improved and reduced water solubility, respectively, and the former was shown to be appropriate for parenteral administration.



Chloramphenicol succinate

5. Reduction of Gastric Irritation

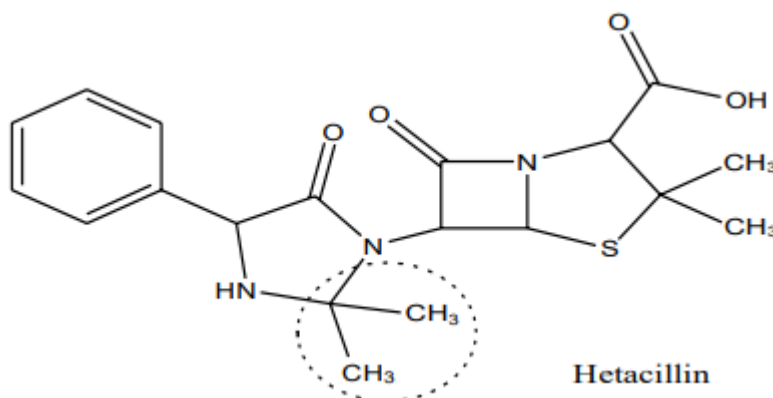
- Aspirin, Ibuprofen and Diclofenac are NSAIDs which possess carboxylic group in its structure, because of free carboxylic group the produces gastric irritation, then by applying the concept of prodrugs the free carboxylic group converted into ester, amide or salt without altering the pharmacological action.
- Diclofenac is generally available as Diclofenac sodium and aspirin itself is a prodrug of salicylic acid.



Aspirin

6. Increase in Stability of Chemicals

- Stability of Chemical substances is very important for therapeutic activity of drug, the concept of prodrug is used to enhance the stability of drug either by modifying the drug's physical characteristics or by altering the functional group that causes instability.
- Hetacillin is a prodrug of ampicillin which is formed by reaction between ampicillin with acetone by which the free amino group of ampicillin cyclized with acetone and produces Hetacillin. This change increases the stability of ampicillin by inhibiting auto aminolysis.



Hetacillin

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